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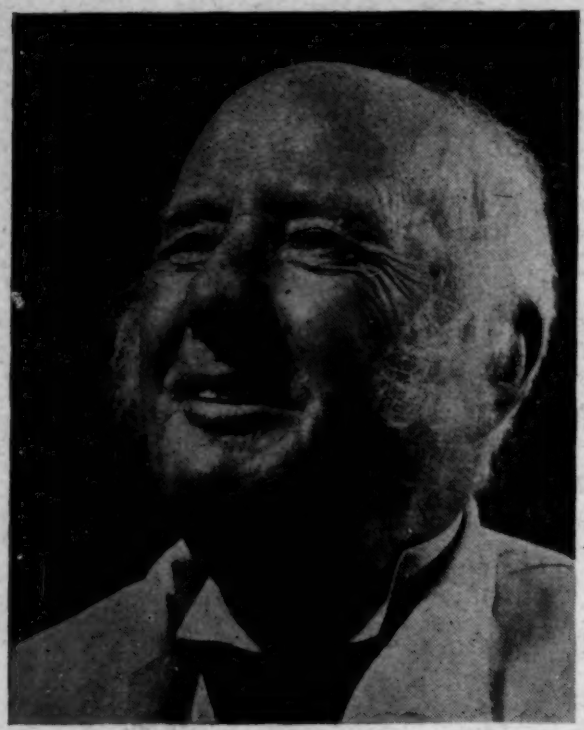

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BRITISH MEDICAL JOURNAL

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TROPICAL MEDICINE—PAST, PRESENT, AND FUTURE*

BY

R. N. CHAUDHURI, M.B., M.R.C.P.Ed., T.D.D., F.N.I.

Director, Calcutta School of Tropical Medicine

I would like to give you a bird's-eye view of the outstanding events in tropical medicine in the latter half of the nineteenth century. It is well to remember that most tropical diseases were once almost as common in the cold as in the warm countries. Let me give a few examples. During the last century there had been at least five epidemics of cholera in Europe, causing millions of deaths. Plague flourished for centuries; the great pandemic that occurred in the fourteenth century was known as the Black Death on account of the terrible toll it took of human lives. Malaria was endemic in England even in the nineteenth century, and severe epidemics have been recorded in Denmark, Holland, and North Germany. Leprosy was for long widespread in Europe, where it still lingers in some places. Yellow-fever epidemics were reported from the eastern states of the U.S.A., but have been practically banished in the last 50 years. Even as late as 1933 there was an outbreak of amoebic dysentery in Chicago with 1,400 cases and over 40 deaths.

As a result of these pestilences and other common diseases there was what we may call sanitary awakening, and people began to associate disease with filth and demanded that something be done to counteract it. In England the Public Health Act, 1848, led to the purification of water supplies and improvement of sewerage, and this was followed by a rapid decline in the two main intestinal infections, typhoid and cholera. This campaign against environmental filth was based on the conception of atmospheric impurities emanating from insanitary privies, etc., and preceded any knowledge of disease germs as causative factors. Another stimulus to the study of tropical diseases came from an entirely different direction—the Europeans' interest in their overseas colonies, where they suffered from these diseases as much as or perhaps more than the indigenous population.

Microbes, Vectors, and Immunity

It was during the last three decades of the nineteenth century that the development of bacteriological techniques and their application led to the unravelling of the aetiology of many infectious diseases. In 1871 the anthrax bacillus was thoroughly studied and proved to bear a causative relation to this disease. Then the investigators turned successfully to other diseases. This was the era of Pasteur and Koch, associated with great activities in the bacteriological field in which many causative agents were recognized and described, including those of leprosy, amoebic and bacillary dysentery, cholera, enteric fever, malaria, undulant fever, and plague. By 1900 the aetiology of most major tropical diseases was known. The discovery of rickettsias and viruses belongs to the twentieth century.

The study of parasitic worms had been initiated by naturalists. One of the parasites, hookworm, is a source of considerable ill-health in the Tropics. Its pathogenicity had been known since 1854. Löose in 1897, in Egypt, accidentally discovered its mode of entry into the human body. The interest aroused by this discovery led to the investigation of numerous worms parasitic in animal and man. Many have been shown to have extremely complex life histories.

No less important was the discovery of vectors and their role in spreading disease from man to man, knowledge of which has made possible the adoption of radical preventive measures. Manson in 1878 made the important observation that *Filaria bancrofti*, which had been known to live in the blood of man, went through part of its development in the mosquito, which served as intermediate host. This was the first time that an insect was shown to be a disease carrier. Manson also formulated the mosquito–malaria hypothesis, and in 1897 Ross, while working in Secunderabad, discovered malaria oocysts in the stomach wall of the anopheles mosquito. The following year, while working in Calcutta, he demonstrated the life-cycle of the allied parasite of birds, the infection being conveyed from one bird to another by the mosquito in the act of biting. Subsequently Grassi, in Rome, demonstrated a similar cycle of development of human malaria parasites in the *Anopheles maculipennis*. Flies, lice, ticks, mites, and fleas have also been traced as vectors of certain diseases.

One important observation made by Koch (after his discovery of *V. cholerae* in Egypt and India) while studying cholera, which is of great epidemiological importance, was that convalescent cases or contacts with minor symptoms were excreting the vibrios. It was thought that these apparently healthy persons might be responsible for outbreaks or spread of the infection when no other obvious cause could be found, and this was soon proved to be the case with other infections. The occurrence of the chronic carrier is now well established in diseases like diphtheria, dysentery, typhoid fever, etc., in which these symptomless carriers form an important reservoir of infection.

Bacteriological researches towards the end of last century led to many results in the laboratory which

*Presidential Address to the Section of Medical and Veterinary Sciences at the 41st Indian Science Congress, Hyderabad, 1954.

have been widely applied. Notably there arose the study of immunity and the development of immunotherapy.

No less important than the triumphs of active immunization was the discovery of bacterial agglutination in 1896 and its application to the diagnosis of typhoid and later of brucellosis and other infections.

Chemotherapy

Up to the first decade of the present century tropical medicine had hardly any specific drugs except quinine for malaria and ipecacuanha for amoebic dysentery. But even towards the end of last century Paul Ehrlich was planning to find synthetic remedies, his aim being that these remedies would be toxic to the parasites but harmless to the patients. His first objective was preparation of an antimalarial drug which would be more potent than quinine, and his choice fell on methylene blue because he had observed that it stained the malaria parasite and that it was harmless to the body. Though its effect was inferior to that of quinine, modern chemotherapy may be said to have been born with this experiment. Later, his effort with a benzidine dye, trypan red, against trypanosomiasis was equally unsuccessful, but it led to a series of researches which culminated, after his death, in the discovery of a complex substance named suramin ("germanin"), still a potent drug for the early stage of this disease. After the failure of trypan red Ehrlich had turned his attention to an organic arsenical, atoxyl, and in 1909 discovered salvarsan, a drug with outstanding activity against spirochaetal infections.

The advances in therapeutics that followed during the next twenty years were many, and mainly benefited tropical medicine. These were saline treatment of cholera, emetine and a number of arsenical and iodine compounds for amoebic dysentery, antimony for kala-azar and schistosomiasis, tryparsamide for trypanosomiasis, and later "plasmoquine" (pamaquin) and "atebrin" (mepacrine) for malaria. But the story does not end here, for now followed an epoch-making period which has benefited all branches of medicine and revolutionized the treatment of most infectious diseases. It began with sulphonamides, and for the first time we had a drug for bacillary dysentery. But the greatest advances were made under the stimulus of war with chemotherapeutic substances quite different from the type envisaged by Ehrlich—namely, antibiotics. The first of these was penicillin, and this was followed by streptomycin, "chloromycetin" (chloramphenicol), aureomycin, "terramycin" (oxytetracycline), and others. We have also got new antimalarial drugs, more powerful than any previously used. Armed with these, we can to-day tackle most infections, including those caused by rickettsiae and some of the viruses. Last, but not the least, is the discovery of insecticides—namely, D.D.T. and B.H.C. (dicophane and benzene hexachloride)—which have rendered the control of malaria and typhus over large areas a matter of simple and inexpensive organization.

I shall now proceed to give a brief outline of the outstanding developments, but as the subject is vast I shall limit myself mostly to the important diseases that prevail in India.

Malaria

Tissue Phase of Parasite

There have been many developments in our knowledge of malaria, which is the most important disease in tropical climates. An outstanding event was the discovery of the tissue phase of the malaria parasite. After Laveran's discovery of the parasite and Ross's description of its passage through mosquitoes, Schaudinn in 1903 reported that he had observed sporozoites of *P. vivax* actively penetrating red blood cells, in which they then developed into the ring form of trophozoites. His account was accepted universally until towards 1930, when doubts began to arise, as some of the observed facts could not be explained in this way. James[1] in 1931 postulated that sporozoites on their entry into the human body passed into the tissues, where they underwent further development before reaching the blood stream. This hypothesis received support when, a few years later, tissue-invading forms of malaria parasite were demonstrated in birds in which the complete cycle was worked out.[2–4] A tissue phase of development in the liver was also demonstrated for the malaria parasite of squirrels.[5 6] It was expected that the malaria parasite of man and monkey would develop along similar lines, but in spite of intensive research in India, Britain, and America no success was obtained until Shortt and his associates,[7 8] in 1948, announced the finding of tissue forms of *P. cynomolgi* in the liver of monkeys; soon after they[9 10] succeeded in demonstrating the tissue stages of *P. vivax* and *P. falciparum* in liver biopsy specimens from volunteers who had previously been subjected to heavy sporozoite infection.

This discovery fills an important gap in our knowledge of the human cycle of the malaria parasite, and it is now evident that parasites pass through a pre-erythrocytic stage of development in liver cells before infecting the red cells and producing clinical symptoms. In the case of *P. falciparum* the initial tissue phase probably dies out soon after the infection has developed in the blood corpuscles, but in *P. vivax* some of the merozoites enter fresh liver cells (e.e. phase) and subsequently produce a second generation of merozoites; this may repeat itself indefinitely and infect red cells at any time, thus giving rise to the relapses of vivax malaria.

Metabolism of Malaria Parasites

More interest is now being taken in the study of metabolism and nutritional requirements of malaria parasites, as this may open up a new approach to successful treatment. But the subject is not so easy, since to gain knowledge of the physiological behaviour of the parasites it is necessary to grow them *in vitro*. After the introduction of newer methods for the successful growth of *P. knowlesi* we recently attempted to cultivate the human malaria parasites, but with little success. Some workers are trying to find out if there is any correlation between the chemical constitution and activity of antimalarial compounds on the enzyme system of parasites. Meanwhile, two interesting observations have been made.

First, the effect of starvation on *P. berghei* in albino rats and mice.[11 12] When the animals were kept fasting only a few parasites appeared in their blood, but when they were fed again the parasites grew normally. Our results were similar to those of Geiman and McKee[13] in monkeys infected with *P. knowlesi*. It is of interest to recall that a similar adverse effect of starvation was observed on the growth of human malaria parasites during the Bengal famine in 1943.[14–16] It was found among sick destitutes that so long as their condition was low they were often afebrile, with a few or no parasites in the blood, but the fever and parasitaemia became manifest in many as soon as their general condition improved with nourishing diet in the hospital.

Secondly, Maegraith *et al.*[17] and Bray and Garnham[18] have observed the suppressive activity of milk on *P. berghei* in rats and *P. cynomolgi* in monkeys. Hawking[19] attributes it to the lack of *p*-aminobenzoic acid (P.A.B.A.) in milk. Variable suppressive results were obtained in our animal and human experiments with milk, but failures were also noted.[20 21] Addition of P.A.B.A. or certain other growth factors did not seem to increase the intensity of the infection. These investigations are still in the preliminary stage, but they may reveal some weak points in the parasites where attacks may be successfully delivered.

Mosquito Eradication

In the past attempts were made to eradicate malaria by destruction of larvae by methods such as canalization of streams, oiling, and application of Paris green. These were relatively inefficient and costly. At a later date came "species control" by which selective measures were taken

to prevent the breeding of only the dangerous species of mosquitoes, being based on an intimate study of the habits of the carrier species. This method has been successfully employed in several places. A biological method is the use of certain kinds of fish—for example, *Gambusia affinis*—which devour mosquito larvae voraciously. Pyrethrum spray to kill mosquitoes was a further improvement. D.D.T. or B.H.C. is now being employed for this purpose, and these substances have the advantage of being non-volatile, so that when sprayed on the walls and ceilings of dwellings they persist as a fine crystalline deposit for a few months and poison mosquitoes that come in contact with them. But the basis of all control is a knowledge of the behaviour of the mosquito. Thus, while D.D.T. kills mosquitoes which alight inside the hut, it is quite harmless to other species which habitually fly in and out without settling except when biting. In some cases B.H.C. has given better results than D.D.T. D.D.T. dissolved in oil can also be used as a larvicide. At present D.D.T. is generally employed in destroying adult mosquitoes, occasionally combined with the other methods mentioned above.[22–24]

Treatment of Malaria

For three centuries quinine and other cinchona alkaloids were the only drugs available against malaria, and they held their place even up to the first quarter of this century. Since then various synthetic drugs have appeared, including pamaquin, mepacrine, chloroquine, amodiaquine ("camoquin"), proguanil ("paludrine"), and pyrimethamine ("daraprim").

The appearance of a number of antimalarial drugs raised the question of their choice in treatment, as the initial claims based on animal experiments and preliminary clinical trials have not always stood the test of time. The ideal drug acting on the different stages of the malaria parasites has yet to be found, but, even as it is, the action of some drugs varies with different species and strains of parasites, and the appearance of drug-resistant variants is another difficulty. It was therefore necessary to assess the therapeutic and prophylactic value of the drugs under Indian conditions, and this work was taken up by us on patients admitted to hospital and in some hyperendemic malarious villages near Calcutta.[25–28] In spite of the development of the newer drugs the efficacy of quinine cannot be questioned, and parenteral quinine still remains the drug of choice in pernicious malaria.

Mepacrine is as effective as quinine, but occasionally causes unpleasant symptoms if given in large doses and for prolonged periods. High hopes were at first raised about proguanil, and it was reported to have an action on the pre-erythrocytic phase of parasites, thus acting as a causal prophylactic.[29] Later experience,[25 30 31] however, showed that it has disadvantages, the chief being that it is slow in action and some strains of parasites are resistant to it.[32–36] We have also demonstrated this by passaging the parasites from one volunteer to another and administering proguanil to each. In view of this, it will be extremely unwise to rely on proguanil alone for the treatment of severe falciparum infection.[37 38] It was also claimed that proguanil prevents the development of sporozoites in the mosquito, but recently we have been able to produce infective mosquitoes after feeding them on patients on proguanil treatment, and to transmit the disease.[39] Chloroquine[40] and amodiaquine[41 42] have been found to be very potent drugs which promptly terminate a clinical attack and are effective even in single doses.[43] With these two drugs it may be possible to introduce a one-dose regimen of treatment among semi-immune people. However, this may not be enough for severe cases and for radical cure. The action of the new drug pyrimethamine[44 45] is uncertain in falciparum infection, and therefore cannot be relied upon for the routine treatment of malaria. It has been suggested that cross resistance between proguanil and pyrimethamine[46] may explain the failure in some cases, though all are not agreed on this point.[47]

Vivax relapses are still a problem, but it is difficult to assess the relapse rate after treatment with a drug unless the trials can be undertaken in suitable non-endemic sites and followed up properly. None of the above drugs, even the most potent of them, when used alone, would radically cure relapsing vivax malaria. But better results are obtained by combining a schizonticidal drug, like quinine or chloroquine, with pamaquin or primaquine, which in itself is a poor schizonticide but active against tissue forms of *P. vivax* that harbour infection between relapses. Its efficacy was amply proved in the Korean war, and we found a very significant reduction of vivax relapses with Indian strains of parasites.[48]

Drug Prophylaxis of Malaria

No drug is yet available which will prevent infection taking place when a susceptible person is bitten by a mosquito, but the existing drugs can prevent the infection from developing into the clinically recognizable disease. Great credit is due to Fairley and his colleagues for their researches during the war, which showed that with small daily doses of mepacrine it was possible to live in a hyperendemic area without getting overt attacks of malaria. Since then drug prophylaxis has been given trials in civilian practice with excellent results. We have carried out mass prophylaxis in malarious villages for five consecutive years during the transmission season without any anti-mosquito measures, with weekly dose of proguanil, chloroquine, amodiaquine, and pyrimethamine, and compared the results with similar groups receiving no treatment at all or at best occasional doses of quinine.[25 49 50] All the four drugs decidedly reduced the incidence of malaria and improved the health of the people, proving unquestionably effective as suppressive drugs. Proguanil is cheap and useful provided drug-resistant variants do not emerge, but the most potent suppressive drugs were found to be chloroquine and amodiaquine. The latter was as effective when administered at fortnightly intervals.[51] A village farm-worker taking it regularly every fortnight during the malaria transmission period may pursue his work without being laid down with malarial attacks during the period.

With the development of primaquine for the ultimate eradication of established vivax infections, mechanisms are at hand for simple and essentially complete chemotherapeutic control of malaria, which should go far towards minimizing its ravages until such time as insect vector eradication becomes a reality on a wide scale.

Kala-azar

Since the eighteen-sixties kala-azar has been known as a very deadly disease, endemic in Bengal and Assam and assuming periodical epidemic proportions. The actual cause of the disease was unknown till the beginning of this century, when in 1903 its mystery was unravelled by the discovery of the causative organism independently by Leishman and Donovan. In 1904 Rogers cultivated the parasites and described the flagellate form. But the transmission of kala-azar remained an unsolved problem for a long time. Knowles *et al.*[52] first brought forward evidence to incriminate the sandfly as the probable vector, but it took 25 years of research to establish that the sandfly could transmit visceral leishmaniasis to susceptible animals and to human beings.[53–55]

But long before this the remedy had been found in a salt of antimony. In 1913 Vianna had tried intravenous injections of tartar emetic and successfully treated South American muco-cutaneous leishmaniasis. In 1915 Rogers obtained very encouraging results in Indian kala-azar. The most important advance was the introduction of pentavalent aromatic antimony compounds, in the development of which the contribution of Brahmachari[56] is so well known. It raised the cure rate to 95% in Indian kala-azar, which had a mortality as high as 90%. This is a truly remarkable achievement. A number of these compounds are available

for intravenous and intramuscular injections.[57–62] The next advance came in the form of aromatic diamidines,[63–67] which gave very good results, but which owing to some unpleasant sequelae, especially with stilbamidine,[65] are used for antimony-resistant cases and those complicated with pulmonary tuberculosis.[68] The treatment of cancrum oris, the most deadly complication, has been found to be satisfactory with penicillin plus specific treatment.[70]

In the diagnosis of kala-azar, besides demonstration of parasites, the aldehyde test and Chopra's antimony test are well known, but for early diagnosis the complement-fixation test, using an antigen prepared from certain acid-fast bacilli,[71] has proved to be of great value, although positive reaction may occasionally be obtained in tuberculosis and leprosy.

Kala-azar, which in the early 'eighties was depopulating Assam, can now be easily diagnosed and cured in the vast majority of cases. But a proportion of cases prove resistant to treatment, and these and the dermal cases serve as a reservoir of infection to the community. In spite of mass treatment campaigns for over 30 years in Assam, the disease still persists.[72] It is, however, probable that if anti-sandfly measures are adopted simultaneously better control may result.

Dysenteries

Bacillary dysentery can now be promptly cured by sulphonamides, and the use of antiserum has been abandoned except perhaps in some severe shiga infections. Streptomycin and the newer broad-spectrum antibiotics offer no advantage over sulphonamides but may be needed occasionally, as in a case of post-dysenteric arthritis, in which we gave streptomycin with excellent results after sulphadiazine had failed.[73]

Amoebic dysentery, acute or chronic, is probably the commonest intestinal disorder of the Tropics. From an analysis of 9,015 unselected cases admitted during ten years to the hospital of the Calcutta School of Tropical Medicine[74] we found that 26.2% were harbouring some protozoa in the intestine, and 8.8% had *E. histolytica* infection. Of the patients who harboured amoebae, 51% came with abdominal symptoms—some typical, some quite vague; while the other 49% were admitted for various other diseases. The latter were apparently carriers of infection or in a quiescent phase. Symptomless cyst-passers are quite common and B. M. Das Gupta[75] found *E. histolytica* in 10.87% of an unselected population in Calcutta. The pulmonary form of amoebiasis,[76–78] either primary or secondary to liver abscess, is apt to be mistaken for tuberculosis but clears up with emetine injections. Similarly, amoebic granuloma or amoeboma[79 80] is apt to be mistaken for carcinoma, and in one of our cases the two were actually associated.[81]

Since the introduction of emetine, acute amoebic dysentery has been readily amenable to treatment, but results in chronic cases are often poor. This difficulty has been at least partially overcome by the introduction of compounds of emetine, arsenic, and iodine. The number of amoebicidal drugs is increasing every day, and we have now aureomycin, oxytetracycline (terramycin), and a few others added to the list. The importance of eradicating secondary infection in chronic amoebiasis was recognized at the Calcutta School of Tropical Medicine many years ago, and bacterial vaccines were advocated.[82] The concept was revived by Hargreaves,[83] who advocated penicillin and sulphonamide for the purpose, but now an initial course of aureomycin or oxytetracycline would serve the purpose. We have tried all these remedies,[74 84–86] and it may be pointed out that the existence of so many drugs for a single disease suggests that the ideal amoebicide is yet to be found. At present there is a good deal of enthusiasm over the newer antibiotics, but they suffer from the same defects as the older drugs—namely, the initial results are good, but the relapse rate is high. In fact, none of these drugs, given singly, prevents a relapse. For some time past it has become customary to use a combination of drugs, which is often more effective than any one alone.

One of the notable advances at the present time is the very successful use of emetine and chloroquine in amoebic hepatitis and liver abscess.[87–91] Operation is now seldom required except in advanced cases, when aspiration repeated as necessary is usually sufficient, antibiotics being also used to combat secondary bacterial infection. Formerly these patients, with open drainage tubes and slowly dying of secondary sepsis, were familiar but depressing sights in our surgical wards.

Cholera

Since the discovery of *Vibrio cholerae*, its aetiological role has been established. But for the production of the disease other factors, such as gastric secretion and personal susceptibility, as well as the property of the vibrio, are also important. Undiluted gastric juice of normal acidity has been found to kill the vibrios immediately.[92]

Much study has been made concerning the epidemiology and spread of cholera,[93 94] but it is still uncertain how the cholera vibrios persist in the interepidemic period. Some observers believe that the carrier state does not persist and that in the absence of animal reservoir the infection can survive only by case-to-case transference throughout the year. But this is not often apparent, and it has recently been suggested that there is a possible link between the spread of cholera and some aquatic fauna.[95]

The cholera vibrios were the subject of much investigation, and Gardner and Venkatraman[96] made the important observation that the O antigens are the specific ones, and gave a systematic classification of the vibrios. The most important advance was the introduction of hypertonic saline and alkali treatment by Rogers.[97] The efficacy of this treatment cannot be questioned, and is testified by its universal adoption. But with the growth of biochemistry the question of the ideal transfusion fluid for physiological replacement cropped up and it was in an attempt to tackle this problem that we undertook an investigation into the fluid and electrolyte changes in cholera.[98] Plasma volume per kilogram of body weight was found to be below the line of normal regression in all the cases, showing a reduction of 32% of the mean value in the fatal group, in contrast to 20.6% in the survival group. Change in the interstitial fluid in the survival group was less marked, but in the fatal group the mean value was reduced by as much as 39%. With recovery all the body-fluid changes were corrected, and it seems in some cases they were overcorrected owing to excessive saline infusion.

More recently it has been possible to follow accurately the changes in sodium and potassium concentration with the help of a flame-photometer. We found very little change in the plasma sodium and chloride level, suggesting that the loss of fluid in cholera is probably isotonic in nature. But there is usually an initial high level of plasma potassium,[99] which may come down even to subnormal level with treatment, and this may cause prolongation of convalescence. In such cases, if there is free flow of urine, judicious use of potassium salt may be helpful. In uraemic cases there is invariably a very high rise of plasma potassium along with nitrogenous retention, which requires careful handling as it is probably an important contributory factor to their fatal termination. Treatment on the lines suggested by Bull[100] for anuria to maintain fluid and ionic balance may be helpful. In cases in which uraemia terminated favourably the plasma potassium declined rapidly along with the urea concentration in the blood.

No specific chemotherapeutic drug has yet been found effective for cholera. The improvements claimed with sulphonamides could not be confirmed.[101] More recently we have used chloramphenicol[102 103] and oxytetracycline[104] with rapid clearance of vibrios from the stools, but with no effect on the clinical course and mortality. Aureomycin[105] also did not improve the results. So correction of fluid and electrolyte balance still remains the mainstay in treatment.

Typhus Fever

This is a very old disease, but only during this century has it been shown to be caused by rickettsial organisms. Apart from the classical epidemic typhus, other infections occurring in various parts of the world have now been recognized as rickettsial infections. Megaw[106] described in 1917 the first case of tick typhus in India; he himself had been the victim. Scrub typhus is fairly common, but the diagnosis is often missed, being mistaken for "enteric" or other fevers. In Calcutta we have encountered mostly scrub typhus and only a few cases of murine or flea-borne typhus.[107-110 110] Different types of typhus fever have also been described from other parts of India.[111-120] A few cases of Q fever have also been recently reported. Scrub typhus, the most important form of tropical typhus, is caused by the bite of the larvae of mites, the reservoir of infection being mite and certain rodents. During the second world war, when scrub typhus became a serious problem, many unsuccessful attempts were made to incriminate the mite species responsible for causation of the disease in South-east Asian countries. In 1949, Krishnan *et al.*[110] not only successfully developed a technique for breeding large numbers of all mites prevalent in an infected area in the laboratory, but also used them in transmission experiments. They were also able to show experimentally that *Trombicula deliensis* was responsible for the transmission of the disease in Bengal, and that congenital transmission from infected mites to their progeny occurred at least for four generations.

In the matter of diagnosis the Weil-Felix reaction may be equivocal or negative in a certain percentage of cases, when animal inoculation is helpful. Cox's discovery[121] that rickettsiae could be grown in the yolk-sac of fertile hen's egg led to the preparation of antigen for complement fixation and rickettsial agglutination for some types of typhus fever.

In treatment chloramphenicol and aureomycin have given excellent results.[123] In prophylaxis the efficacy of D.D.T. and other insecticides and of mite repellents such as dimethylphthalate was abundantly proved in the war. Vaccine is useful in some types of the infection. Conquest of this once world-wide disease is one of the most gratifying results of modern research work.

Typhoid Fever

Chloramphenicol may now be regarded as a specific form of therapy in typhoid fever,[122] but a loading dose as originally advised is not necessary and may even be harmful.[124] Its indiscriminate use should be discouraged, as it may cause, though rarely, aplastic anaemia, and treatment should usually be started after a definite diagnosis has been made, preferably after the first week, when immune reactions begin. Chloramphenicol does not lessen the need for bed rest and dietetic regime until healing of bowel ulceration has occurred. Typhoid patients are no longer put on semi-starvation diet. In our hospital practice we aim at giving at least 2,000 calories and 1 g. protein per kg. body weight with individual variations.[125 126] Prophylactic inoculation with T.A.B. vaccine is now an established practice. This does not provide absolute immunity, but inoculated persons who acquire the disease suffer rather less severely than the uninoculated.

Leprosy

While leprosy has practically disappeared from the temperate countries where it was once common, it has remained persistently endemic in the Tropics and sub-tropics with varying incidence and severity.

Khanolkar[127] has made an interesting contribution to our knowledge of the early phase of leprosy. He sets out the evidence showing that the leprosy bacillus enters the body through the skin and has a predilection for subcutaneous nerve tissues, particularly early in life. Leprosy is neural in its inception, and *Mycobacterium leprae* first appears in clinical lesions in the small nerve plexuses in the skin, travelling up the finest nerve twigs in an ascending infection. He shows that the development of leprosy depends on the bacilli being able to burst out from the subcutaneous nerve and nerve plexuses of the skin into the dermis. The subsequent extension of the disease is determined by the response of the tissue to its mycobacterial invader. If the tissue response is weak, lepromatous leprosy ensues; if it is vigorous the tuberculoid type is likely to develop.

It has now been clearly shown that all cases of leprosy are not infectious; only those patients in whom bacilli can be demonstrated in the skin and nose by routine methods are regarded as infectious cases. Since the disease is transmitted by prolonged and intimate contact of open cases, control measures must aim not only at treatment of the patients but at adequate segregation of the infective cases. The importance of isolation will be evident from an observation in Bombay that more than one-half of a group of contacts showed clinical suspicion of disease and more than a quarter were bacteriologically positive.[128]

Fifty years ago leprosy was regarded as incurable. The first drug used was chaulmoogra or hydnocarpus oil, an ancient Indian remedy that is still in use with some modifications. The sulphone drugs,[129 130] introduced in 1943, have brought in a new era in the treatment of leprosy, and thiosemicarbazones are of great value.

Plague

In the past a number of epidemics and pandemics of plague have taken a heavy toll of life, but in recent years there has been marked progress in its prevention and treatment. Previously, anti-plague serum was the only therapeutic weapon available, but now even septicaemic and pneumonic cases can be saved with streptomycin and sulphadiazine.[131-134] For prevention, besides improvement in general housing conditions, the use of insecticides and rodenticides and inoculation is effective.[135]

Helminthic Diseases

An important recent discovery in filariasis is the synthetic piperazine compound diethylcarbamazine acid citrate ("hetrazan"),[136] which causes rapid disappearance of microfilariae, though its effect on the adult worm is still inconclusive. But one great advantage is that it can render human carriers free from microfilariae and therefore non-infective to mosquitoes for a long period following a course of treatment which lasts about three weeks. Based on these observations, mass treatment is now being instituted in some countries to render mosquito transmission impossible. This, like the drug prophylaxis of malaria, is possibly an interim measure till extensive insecticide spray can be undertaken. In India, active measures are being taken in Orissa to combat filariasis by spraying with D.D.T. to kill the mosquitoes, by bush clearing, and by prophylactic administration of hetrazan.

The frequency of ankylostomiasis, ascariasis, and other helminthic diseases in the Indian villages calls our attention to the lack of sanitation and hygiene in these areas, and it is only by improving these conditions that we may hope to eradicate these infections completely. Potent drugs now available for their treatment include some indigenous preparations like *Butea frondosa, Embelia ribes,* kamala,[139 140] and cashew-nut-shell oil[141] (discovered recently), but there can be no lasting benefit to the community unless adequate preventive measures are taken simultaneously with the mass treatment of the victims.

Undernutrition

I think I have said enough to give a picture of tropical medicine taking shape with the birth of bacteriology and having a robust growth with the discovery of modes of transmission, reservoirs of infection, and means of eradica-

tion. But in the Tropics there are many other diseases besides those caused by infection, and of these the disorders caused by lack of nutrition rank high.

Experience shows that when the daily calorie intake by adults falls below 2,000 a good deal of weight is lost, mostly in the early stages, but later the body adjusts itself to the changed conditions and there is no longer any loss of weight. Health is not impaired, but there is difficulty at sustained effort. At an intake of 1,500 calories psychological changes manifest themselves in the form of irritability, apathy, and impaired mental concentration. With further reduction in calories a protein-deficiency anaemia appears; later comes nutritional oedema, the onset of which is accelerated by physical exercise. As the shortage continues, nutritional diarrhoea (para-sprue) occurs owing to impaired absorptive power of the intestine, and signs of vitamin deficiency commonly appear. In the absence of such conditioning factor there may be no obvious sign of vitamin deficiency.

In the treatment of starvation great success has attended feeding with skimmed milk and glucose with vitamins. For advanced cases Krishnan *et al.*[142] successfully used protein hydrolysate, made from papain digest of meat during the Bengal famine. A sudden increase of carbohydrate intake, especially of polished rice, may precipitate an acute state of vitamin depletion. During convalescence patients recover best on a mixed diet of high calorie value with light exercise. Supplementary vitamins and proteins have no apparent effect on the pace of recovery.

Vitamin Deficiencies

The main causes of many of these diseases are now known, but it appears that the deficiencies are often multiple, especially where vitamin-B complex is concerned. During the war, in the Far East, where polished rice was issued to prisoners and the diet was generally very poor, there was widespread evidence of vitamin-B-complex deficiency.[143] The onset was often precipitated by diarrhoea and dysentery, and by hard manual work. Apart from polished rice, faulty cooking and dietary habits among rice-eating people may bring about attacks of beriberi, and according to Mahadevan and Raman[144] millet-eating people are not exempt from the disease.

Pellagra has been reported from many places. The reason for its prevalence in maize-eating people is that maize is deficient in nicotinic acid. There are strong reasons for believing that maize contains an anti-vitamin antagonistic to nicotinic acid. Rice can be equally poor in this vitamin, as in the case of milled rice, but the tryptophan it contains can be converted into nicotinic acid in the body. It is probable that in some circumstances this does not happen, thus accounting for occasional cases of pellagra among rice-eating people. We do not yet know why pellagra occurs suddenly in a group of people, disappears, and then recurs after a time.

Among prisoners of war in the Far East were seen many cases with grossly abnormal neurological signs such as retrobulbar neuritis, nerve deafness, spastic paraplegia, and rarely paralysis of vocal cords. As they occurred often in association with or after attacks of beriberi or pellagra they were thought to be of nutritional origin, but the results of treatment with good food and vitamins were disappointing. One very distressing condition was burning feet, which was worse at night, causing insomnia. It seems to be not uncommon in India, especially in the south.[145]

It often happens that in the midst of multiple deficiencies the signs and symptoms due to one particular vitamin predominate. We do not know why. In fact, the more one studies these deficiency diseases the more one is convinced that a lack of vitamin, though of fundamental importance, is not the whole story, and that a variety of stresses and strains determine the body's requirements of these essentials. The same observation was made 200 years ago by James Lind, who first clearly proved that scurvy among ship's crews could be relieved by the juice of citrus fruits; he emphasized that its aetiology was inseparably connected with the sailor's life at sea, including cold, damp, infection, and fatigue—factors now called "stress."

Protein Deficiencies

In the dietary treatment of many diseases emphasis is now put not only on calories but also on protein, because the latter is needed for repair. In addition, lack of protein in itself may bring about disease. In prolonged fevers it is essential to cover the protein losses with nutritious food so far as possible.

Kwashiorkor[146–148] is a disease of young children among the very poor class of people who are on a high carbohydrate diet lacking in essential amino-acids. Its chief features are growth retardation, dyspigmentation of hair and skin, oedema, low serum albumin, negative nitrogen balance, and fatty infiltration of the liver. The general opinion is that it is mainly due to lack of protein, especially at the time of weaning. Proteins (particularly animal protein) are remarkably curative in the early stages.

Anaemia among the general population and in pregnant women remains an important problem in India. Addisonian pernicious anaemia is very rare there, but nutritional macrocytic anaemia simulating pernicious anaemia is, on the other hand, very common, and is often accompanied by megaloblastic bone marrow. It usually responds well to crude liver extract, folic acid, and vitamin B_{12}. Folic acid deficiency is apparently the main pathogenic factor, but deficiency of vitamin B_{12} also seems to be present.[149] In addition it is frequently associated with iron deficiency, producing a picture known as dimorphic anaemia.

Nutritional deficiencies have recently attracted much attention as a possible cause of organic disease of the liver. In kwashiorkor, pellagra, chronic alcoholism, and many other conditions there is a slowly developing diffuse cirrhosis of the liver, preceded by fatty infiltration, which takes place in the absence of lipotropic substances such as choline and methionine. Until recently a diet chiefly carbohydrate in composition was recommended in hepatic disease, as throwing least strain on the damaged organ. Animal experiments tend to show that this view is probably wrong and that protein in liberal amount, especially as skimmed milk (a rich source of methionine), should be given along with carbohydrates.

Nutritional oedema has received much attention since the war. Our own observations[150] on nearly 100 cases during the last two years showed that these poor patients lived on a diet grossly inadequate, both in quality and in quantity, in calories and proteins. Previous gastro-intestinal disorder might be an important contributing factor. The severe cases had generalized oedema, low urinary output, steatorrhoea, anaemia, and appreciable diminution of plasma proteins and albumin fractions. In the course of the illness there seemed to be considerable disturbance in the body-fluid compartments,[151] the plasma volume being reduced and the thiocyanate space much increased; the latter persisted for some time even after the disappearance of clinical oedema.

Diseases Caused by Food Adulteration

Argemone Oil Poisoning

Of the diseases caused by food-poisoning, epidemic dropsy stands foremost; it is caused by ingestion of edible oils which have been contaminated with argemone oil. The latter is a toxic agent derived from the seeds of *Argemone mexicana*, which grows as a weed. These seeds are very similar to the dark-coloured mustard seeds, and may be mixed up with the latter by design or accident in the manufacture of mustard oil. Contamination of sesame oil and groundnut oil has also been reported. The disease is encountered periodically in Bengal, but occurs also elsewhere in India. Recently there was an outbreak in Bombay (Nadiad district). It may be conveyed otherwise than through oil, as not long ago there was an outbreak in South Africa which was traced to wheat and argemone seeds getting mixed up by accident.

The toxic property of argemone oil was known as long ago as 1878, when accidental poisoning from the use of this oil in food was reported in a number of cases.[152] In 1926 S. L. Sarkar[153] reported symptoms of epidemic dropsy, in some cases resulting from the use of mustard oil adulterated with *katakar* or argemone oil, and in 1937 Lal and Roy,[154] and later Chopra *et al.*[155] reproduced the early stages of the disease in some instances by feeding human volunteers with the toxic oil. Later, experimental studies on animals were started by us which led to some important observations. An epidemic dropsy-like condition with similar histological appearance and vascular pattern was produced in monkeys fed or injected with argemone oil,[156] and rice diet appeared to favour the accumulation of extracellular fluid.[157] The oil was found to be toxic even in very low concentrations, 1% or 0.5%, after prolonged ingestion.[158]

Work has subsequently been started with argemone alkaloids, of which a much greater yield of the different fractions could be obtained by a newly developed method of direct extraction from the seeds than from the oil.[159] S. N. Sarkar[160] has isolated the alkaloids sanguinarine and dihydrosanguinarine. He regarded the former, constituting only 5% of the total alkaloids, as the toxic agent; dihydrosanguinarine, comprising 87%, appeared to be non-toxic, but was readily oxidizable *in vitro* to sanguinarine, and 8% of the alkaloids still remains unaccounted for. Our biochemical investigations in this condition showed increase of plasma chloride and blood pyruvic acid with a lowering of plasma albumin and absence of thiamine deficiency. The plasma volume and extracellular fluid volume were always increased and the total red blood cell mass was contracted.[161] Based on these results, a high-protein/salt-poor diet with a moderate amount of fat and carbohydrate has been advocated.[162]

A disease such as this which can cause high mortality, seriously affect the heart[163 164] and eyesight, and cause abortion of pregnant women, deserves serious notice, especially when its aetiology is known. Strong public-health measures should be taken to stop the contamination of the cooking oils by argemone oil. The heavy percentage of the latter in many samples of mustard oil points to deliberate contamination. A simple sensitive test has been devised by us to detect the adulteration.[165]

Mineral-oil Poisoning

Mineral oil is another menace to public health. It is a petroleum product, easily available, cheap, colourless, tasteless, and almost odourless, and therefore is an attractive adulterant for edible oil. We therefore undertook an investigation of this oil and found it toxic and often lethal to the animals tested.[166] Histological studies of animals showed vascular changes of the same nature as in argemone poisoning.

In England and the U.S.A. during the late war, when fats were short, mineral oils were used in making cakes, in salad oil, and for cooking chipped potatoes, but the practice has since been prohibited. Several workers[167] have shown that continued ingestion of such oils interferes seriously with absorption of fat-soluble vitamins and of calcium and phosphorus. It has also been observed that some of the oil may on absorption be carried and deposited in distant organs such as lymph nodes and liver[168]; the fate of such deposits is not known. The question of carcinogenesis has been raised but not settled.[169] But what we know already about mineral oil is enough to condemn it for regular human consumption.

Conclusion

I have attempted no more than a brief and fragmentary survey of the progress of tropical medicine. There has been, especially during the last half-century, brilliant and co-ordinated work by individuals and teams of workers directed to the investigation, prevention, and cure of disease. Too high praise cannot be given to the pioneers, who often worked in adverse circumstances, sometimes at the expense of health and even life. But our problems are still many. As old problems are solved new ones arise. Viruses have assumed a great importance in recent years, and cancer is becoming increasingly prominent.

Before I end, however, I should like just to consider what the term "tropical disease" really means. There are not many diseases peculiar only to tropical climates, although admittedly conditions in the Tropics are more favourable to their growth and spread. Such devastating diseases as cholera, smallpox, plague, malaria, and leprosy that now prevail here were, as I have already pointed out, once very common in Western countries. If taken in the sense of latitudes, labels such as "tropical diseases" and "tropical medicine" are largely misnomers; what is worse, they perpetuate a false idea that tropical countries, try as they may, are doomed always to suffer from these diseases. "Tropical" diseases disappeared from the West mainly for three reasons: first, better and abundant food as a result of better cultivation at home and the importation of food from overseas; secondly, the removal of poverty as a result of the industrial revolution and the acquisition of colonies; and, thirdly, the institution of public-health measures, which led to better housing and hygiene, improved sewerage, and a safe water supply. If we consider "tropical disease" in this light much of it is reduced almost to "poverty disease." In short, many of our so-called tropical diseases are the symptoms of backward countries and not primarily of tropical climates. Remove food deficiencies in the tropical countries and introduce all the sanitary measures now enjoyed in the West and many of the tropical diseases will be banished. Our knowledge of these diseases, their prevention, and their cure has advanced to a remarkable degree; in fact, it has outstripped its practical application. With a parallel improvement in social and economic conditions, there is little doubt that our efforts to eradicate them will be crowned with success.

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APLASTIC ANAEMIA DUE TO TRINITROTOLUENE INTOXICATION

BY

M. A. DOBBIN CRAWFORD, M.D., F.R.C.S.I.
Assistant to the Chief Medical Officer, Ministry of Supply

Trinitrotoluene (T.N.T.) is the most generally used of all chemical war explosives. Used alone, or mixed with other compounds, it forms the bursting charge in shells, mines, and bombs. The filling of these weapons of war is still largely done by hand, with the use of tools made of wood or non-ferrous metal. A main preoccupation of the medical officer in an explosives filling factory is the protection of the workers from absorption of T.N.T. Unfortunately, this material finds ready entrance to the body, whether in the form of fume or dust, mainly by inhalation, but also by ingestion and through the skin. When the dose is small and the body healthy, T.N.T. is rapidly detoxified in the liver, the metabolic products are excreted mainly by the kidneys, and no appreciable harm is done. When, however, the dose is larger, or for some reason the detoxifying mechanism in the body is unable to cope completely with the invasion, then T.N.T. or, more probably, the early and even more poisonous products of its metabolism (Channon *et al.*, 1944) accumulate and circulate in the blood stream, inflicting damage upon susceptible tissues.

The clinical manifestations of T.N.T. intoxication are six in number: cyanosis, dermatitis, anilism, toxic jaundice, toxic anaemia, and toxic purpura, roughly in this order of frequency. Each may appear separately from the rest, or in varying combination, simultaneously, or in processional order. The only exception is T.N.T. dermatitis, which rarely, if ever, is present in conjunction with the more serious developments. This paper puts on record all the cases of toxic anaemia and toxic purpura due to T.N.T. which occurred in the United Kingdom, and were noted, during the 1939–45 war.

Toxic anaemia was first made notifiable in January, 1942. Some 15 cases, all ending fatally, were recorded

during the first world war, and the majority are noted in the *Proceedings of the Royal Society of Medicine*, 1917, Vol. X, where a symposium on the effects of T.N.T. is reported. Further comments may be found in the Medical Research Council Memorandum, Special Report Series No. 58, 1921.

During 1939 no toxic anaemia was noted amongst T.N.T. workers in the United Kingdom. In 1940 there was 1 case, which recovered; in 1941 there were 8 cases, with 6 deaths; in 1942, 9 cases, with 3 deaths; in 1943, 4 cases, with 3 deaths; in 1944, 3 cases, with 2 deaths; in 1945, 1 case, which recovered; in 1946, 1 fatal case. A total of 27 cases and 15 deaths.

Of these 27 cases 3 were atypical, mild in degree (early ?), but the remaining 24 were all diagnosed as aplastic anaemia due to T.N.T.—9 of these persons recovered and 15 died.

Effects of T.N.T. Upon the Blood and Bone Marrow

The assimilation of T.N.T. results in a variable degree of anoxaemia. There may be a haemolysis of some of the red cells circulating in the blood stream; in other erythrocytes the haemoglobin may be destroyed in the cell; others are

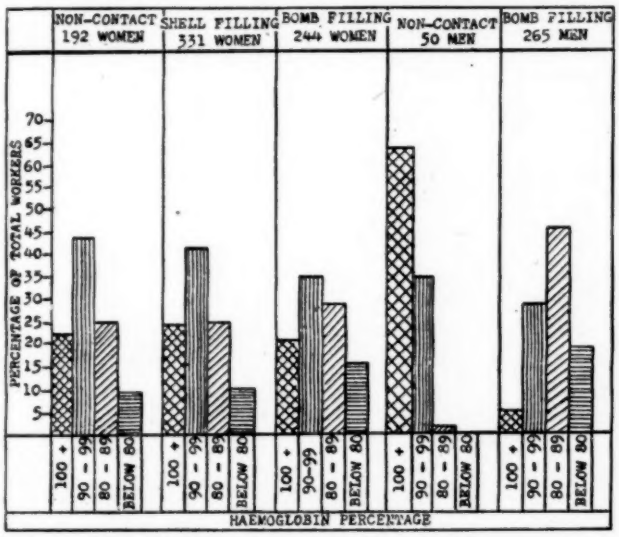
NON-CONTACT 192 WOMEN
SHELL FILLING 331 WOMEN
BOMB FILLING 244 WOMEN
NON-CONTACT 50 MEN
BOMB FILLING 265 MEN
PERCENTAGE OF TOTAL WORKERS
100 + 90 - 99 80 - 89 BELOW 80
HAEMOGLOBIN PERCENTAGE

FIG. 1.—Haemoglobin percentage of T.N.T. workers and controls in a Royal Ordnance factory, 1944. (Haemoglobin estimation by Haldane and Sahli.)

temporarily deprived of their oxygen-carrying capacity by the formation of methaemoglobin, and yet others suffer a permanent fixation of their pigment in the form of sulphaemoglobin (Jope, 1946).

A slight degree of anaemia may persist for some weeks or months while the bone marrow maintains its capacity to restore the blood cells to their normal strength when absorption of T.N.T. has ceased. A decrease of 10% in the haemoglobin commonly occurs, but any further diminution calls for investigation (Ramsay, 1946) (Fig. 1).

At the same time, however, the marrow is affected by the circulating poison. The first reaction is a stimulation of the haemopoietic tissues: the bone marrow becomes hyperplastic, and to a surprising degree—the shaft of the femur and the ribs and vertebrae have all been found filled with active red marrow. There is an increase in the number of reticulocytes circulating in the blood stream, and a moderate leucocytosis; the monocytes may be increased in number (Hamilton, 1946). A slight increase in the size of the red cells may be observed. The reticulocytes were estimated in 184 workers exposed to T.N.T. (Ramsay, 1946). In 20% of these there were more than two reticulocytes per 100 red cells; these counts are probably associated with some hyperplasia of the marrow, and such workers should be most carefully watched, for it must be remembered that reticulocytosis has been found to increase greatly after workers have been removed from contact (Stewart *et al.*, 1945).

With further intoxication, the blood-forming tissues begin to fail, the marrow itself becomes hypocellular, and the cells in the blood are reduced in number. "There is a profound normocytic anaemia with agranulocytosis and a low platelet count. All the blood-forming elements are affected" (Lane, 1942). The casualties cannot be replaced, and a progressive aplastic anaemia develops, which in three of every four cases known in the United Kingdom has ended fatally. The hazards of such an aplastic anaemia are very great. Although by sufficient and repeated blood transfusions the patient may be kept alive, there is no certain favourable prognosis until the blood-forming function of the marrow has been actively restored. During the months or years which may elapse before recovery is fully attained, prognosis must be guarded—a crop of boils, a septic tooth, an acute infection of the tonsils, an attack of influenza, or even perhaps an injudicious dose of sulphonamide may at any moment bring catastrophe.

It has been said that all elements of the blood are affected, but the degree to which each type of cell suffers is very variable. It is rare to find that the white cells are only little affected when the red cells are depleted. In many cases a neutropenia is the most marked effect, proceeding to agranulocytosis, while in others it is chiefly the platelets which have suffered loss—a low platelet count with increased fragility of the capillaries becomes established, and the condition is one of toxic purpura.

Deterioration is rapid, particularly when the anaemia is associated with a thrombocytopenic purpura. In these cases the decline is lamentably swift.

Toxic purpura has been associated with aplastic anaemia in the most severe intoxications. A purpuric eruption has also been noted at necropsy in the majority of deaths from toxic jaundice due to T.N.T.

The low incidence of intoxication amongst the thousands of workers exposed to T.N.T. was undoubtedly due to careful pre-employment examination, the unfit being rejected, and to the precautions taken to prevent any undue absorption of the fume or powder. It is clear that in healthy individuals, constantly exposed to a not excessive dose of T.N.T., a tolerance can be developed: detoxification is adequate, the marrow responds to the call for an extra supply of cells to the blood, and a serviceable equilibrium is

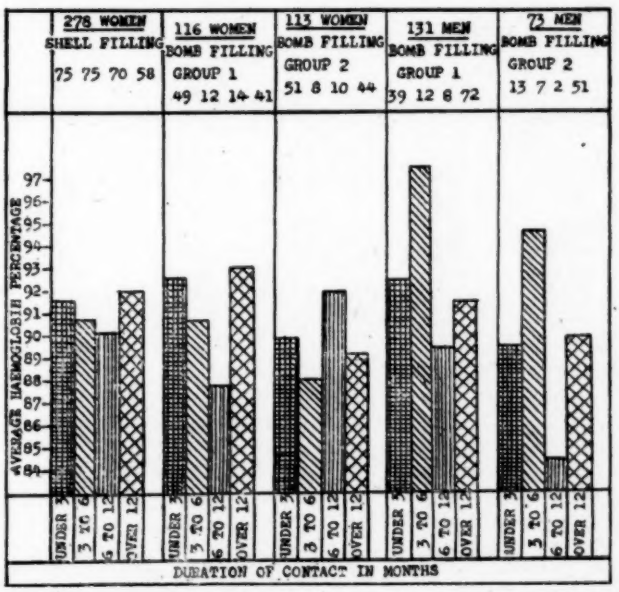
278 WOMEN SHELL FILLING 75 75 70 58
116 WOMEN BOMB FILLING GROUP 1 49 12 14 41
113 WOMEN BOMB FILLING GROUP 2 51 8 10 44
131 MEN BOMB FILLING GROUP 1 39 12 8 72
73 MEN BOMB FILLING GROUP 2 13 7 2 51
AVERAGE HAEMOGLOBIN PERCENTAGE
UNDER 3 3 TO 6 6 TO 12 OVER 12
DURATION OF CONTACT IN MONTHS

FIG. 2.—Average haemoglobin percentage of workers in T.N.T. for varying periods in a Royal Ordnance factory, 1944. (Haemoglobin estimation by Haldane and Sahli.)

established. This was confirmed by the late Helen Ramsay when, in 1944, she determined the haemoglobin percentage in 785 workers in contact with T.N.T. and in 242 controls who were not exposed to this compound. In four of the five groups examined the haemoglobin percentage was higher in those who had been exposed for over a year than in those who had worked in contact for 6–12 months (Fig. 2).

Condition of the Blood in 27 Cases

The blood picture produced by the impact of T.N.T. was aggravated in many of these cases by the resulting haemorrhages. Haemorrhages were noted clinically in 11 of the fatal cases and in three of those who recovered. Haemorrhages were found after death in three other cases (in two of these clinical records are not obtainable). Bleeding from the gums and from the nose occurred most frequently; there were retinal haemorrhages in three cases, conjunctival haemorrhages in two others. Menorrhagia occurred in two cases, and in one other there was uterine haemorrhage so severe that it led to a mistaken diagnosis of abortion and the uterus was explored and emptied—of blood clot only. Such an error occurred in two cases during the first world war (O'Donovan, 1921).

Red Blood Cells

Number.—The counts recorded were: 630,000 per c.mm., the lowest count, in a fatal case; 730,000, the lowest count recorded with recovery; 1,000,000 or fewer in 7 cases; 1,500,000 or fewer in 18 cases; 3,000,000 or fewer in 23 of the aplastic anaemia cases (no record in one case). The three milder cases of toxic anaemia were found to have their red cells reduced to: 3,380,000, 2,790,000, and 3,504,000 per c.mm.

Size.—The anaemia was normocytic or macrocytic. Anisocytosis was recorded in 14 cases; in 12 of these, red cells larger than normal were seen (taking the normal mean corpuscular diameter as from 6.6 to 7.7 μ). Eight cases showed macrocytes of diameter up to 8.4 μ, two of them showing megalocytes up to 10 μ in diameter; of these two cases, one recovered, while in the other a terminal examination before death found red cells of 12.5 μ and even 15 μ in diameter. In both, occasional microcytes, diameter 5 μ, were found. In three other cases macrocytosis was noted, but the size of the cells was not recorded; and in yet another case "a few megalocytes and microcytes were seen."

Immaturity and Other Variations—Occasional erythroblasts were seen in two cases. Films were stained for reticulocytes in only a few cases, and the numbers recorded varied from nil to 4% of the red cells. Polychromasia was noted in only five cases, three being fatal. Poikilocytosis was recorded in only seven patients, being marked in two (three died, four recovered). Stippled cells were found in one fatal case and in one which recovered. Target cells were seen in four cases; three were not cases of frank jaundice.

Haemoglobin.—In some of the patients who died the haemoglobin fell to a very low level—12% in one, 14% in one, 17% in one, 20% in one, 21% in two—and was present in varying quantity up to 45 and 50% in the remainder (7) of the 13 fatal cases in which the blood was examined. In those who recovered, the lowest Hb content recorded was 17% in one case, 18% in one, 20% in one, 28% in one, and varying up to 70% in the remaining eight.

The colour index was at some time raised in the great majority of these patients, the figure varying from 1 to 1.5. In three cases only was the colour index below 1 at every count; one of these three had been ill with T.N.T. jaundice previously, one had been dosed with sulphonamide, and one had the complication of a chronic nephritis.

White Blood Cells

In the 13 fatal cases in which the blood was examined the white cell count varied from 300 to 4,800 per c.mm. (2,800 or less in eight cases), with the exception of one girl for whom a differential cell count was done only once, the white cells numbering 6,200 per c.mm.

The white cell count in the nine patients who recovered varied up to 5,200 per c.mm., the lowest recorded being 2,000 (one case) and 2,200 (two cases).

The three cases of milder toxic anaemia showed on admission white cells of 7,400, 10,000, and 12,000 per c.mm. In each the number of white cells diminished during convalescence and recovery, although the last case (12,000), when seen one year and nine months later, was found to have 15,600 white blood cells. This young woman, however, had some chronic infection, variously diagnosed as an appendicitis and a cervicitis with pelvic infiltration.

The differential white cell count was recorded in only 12 of the fatal cases.

Polymorphonuclear Leucocytes.—These amounted to: from nil to 4% of the white cells in four cases (agranulocytosis), 7% in one case, 18–25% in six cases, and 62% in one case in which there were massive haemorrhages. In a thirteenth case it is recorded that more lymphocytes than polymorphs were seen. In the nine patients who recovered, the lowest neutrophil count varied between 28 and 84%.

Lymphocytes.—In nine of the fatal cases the highest number of the lymphocytes in the blood stream varied between 61 and 92% of the white blood cells, the average being 78%. In a tenth case it is simply stated that the lymphocytes were more numerous than the polymorphonuclears. In one case they numbered 31%; this was the woman with severe uterine haemorrhage. The number of lymphocytes is recorded in seven of the nine patients who recovered. They formed between 40 and 55%, the average being 48%. In the three milder cases of toxic anaemia the lymphocytes formed 19%, 37%, and 35%.

Monocytes.—In 10 of the fatal cases monocytes varied between 3% and 9% of the white blood cells, and in the aplastic anaemia patients who recovered, between 2 and 8%. In the three milder cases the monocytes numbered 1%, 2%, and 10%.

Bone Marrow

Records are scanty. A sternal puncture was done in only three of the fatal cases; in two of these the marrow was aplastic, while in the third the finding was inconclusive. Necropsy reports are available in 12 cases, but in only three of these was the marrow examined microscopically. Macroscopic inspection found the marrow aplastic in every case but one. The exception was that of a young woman who had died of acute purpura following jaundice, and her marrow showed a brisk haemopoiesis.

In the nine patients who recovered, sternal puncture was done in seven: in four of these the marrow was aplastic, hypocellular; in three the marrow showed a hyperplastic reaction.

It is noted that in one patient who died and in one who recovered, the hypoplasia of the marrow chiefly affected the red cells; in three who died there was a marked agranulocytosis; and in one case, also fatal, there was a marked agranulocytosis with disappearance of the platelets.

These findings tally with those of Bomford and Rhoads (1941) in their description of refractory anaemia. They state that cases of toxic anaemia, as formerly described, showed a decrease in erythrocytes, granular leucocytes, and platelets, with the red cells normal in size and shape, and an absence both of signs of regeneration and of immature blood cells; whereas it is now recognized that slight macrocytosis, small numbers of immature red and white cells in the blood, and reticulocytosis are compatible with a severely hypoplastic anaemia.

Condition of the Organs

Liver Damage.—Evidence of liver damage was found in 10 of the 15 fatal cases. Three showed acute liver necrosis at necropsy and one a subacute necrosis of the liver with nodular areas of regeneration. One had jaundice in the course of her short illness; at necropsy the liver was found

to be congested, weighing 56 oz. (1.6 kg.). One was slightly icteric on admission to hospital. In two other cases the liver could be felt two fingerbreadths below the right costal margin (no post-mortem examination in either). In two cases the liver at necropsy showed some fatty degeneration. Of the nine patients who recovered, three showed jaundice at some time. One was slightly jaundiced at the start of his illness, the liver being slightly tender, but not enlarged; another had an icteric tinge in the sclerotics, a weak positive indirect reaction to the van den Bergh test, and a persistent porphyrinuria. The latter patient was a woman who had some epigastric tenderness and whose liver seemed smaller than normal. The third was a girl whose illness started with jaundice. Concerning one other man, who recovered, having been admitted to hospital desperately ill with anaemia, it is noted that eleven months later his liver was found to be enlarged and hard. Of these 24 persons, therefore, 14 gave some evidence of liver dysfunction. The three milder cases, labelled "toxic anaemia," showed no sign of liver damage. In three of the cases noted above, the patient was first admitted to hospital on account of T.N.T. jaundice, and only when the jaundice had disappeared and the patient was apparently mending well was the injury to the bone marrow apparent, or, at any rate, appreciable.

Spleen and Lymphatic Glands.—No significant abnormalities were found in the spleen or lymph nodes of these patients. In one who died the spleen was found to be congested and weighed 4 oz. (113 g.); in another the spleen was elongated but not greatly enlarged, and it is noted that the lymph nodes were "somewhat enlarged and looked haemorrhagic." In yet another it is noted that the spleen weighed 140 g., was dark purple in colour and firm, and the Malpighian bodies were prominent. The lymph nodes were dark in colour but not much enlarged. One other patient who died had caseous tuberculous glands in the chest.

Condition of Heart.—Organic heart disease was discovered after death in one woman—slight mitral stenosis and fibrosis as of healed rheumatism. One other woman who had a blowing mitral systolic murmur showed also clubbing of the fingers. There was slight enlargement of the heart in two cases. Haemic murmurs were noted in five. In two patients the first aortic sound was weak; of these two, one died and haemorrhages were found in the heart muscle, while the other recovered.

Gastric Secretion.—A test meal was given in eight cases. One young man who died was found to have achlorhydria before and after histamine; one woman who died had a low total acidity and low HCl content; one who recovered had no free HCl and a low total acidity; in the other five cases the gastric acidity was normal or high, and, of these, four recovered and one died.

Ulceration about the Mouth and Pharynx.—This condition was present in six cases; two others had a glossitis and a ninth had preliminary dental sepsis, treated by extraction and dosage with sulphonamide.

Signs and Symptoms of Toxic Anaemia

Toxic aplastic anaemia has a most insidious onset. It should be emphasized that the expected signs and symptoms of severe anaemia may be appreciated only at a very late stage—pallor, fatigue, giddiness, breathlessness on exertion, abdominal pain. Pallor is certainly present, but may be unnoticed; fatigue and lassitude are usually present, but have not been taken as a danger signal, being the common lot in wartime. In the eagerness of wartime effort and the insistence of domestic anxieties, workers will not complain of even severe malaise. Sixteen of these persons complained of marked fatigue; they felt "always sleepy and weary," "sleepy and lifeless," "terribly tired," but the majority made such complaint *only after admission to hospital.* In the same way, 11 confessed to a shortness of breath, but most of them made this confession in a hospital bed. Cyanosis was noted only in six cases, and it was slight in all but one of them. Only one, a woman, showed the typical ashen-grey pallor of anilism. Loss of weight may not be striking; one woman thought she had lost weight. Another, on admission to hospital, weighed 6 st. 3¼ lb. (39.6 kg.), having had a serious loss of weight: she "could wrap her coat around her twice." She gained 3 st. (19 kg.) during her 14 weeks in hospital. Headache started off the illness in two cases. Paraesthesiae are not uncommon. Two patients first consulted their own doctor on account of neuritis; another complained of cramps in his legs.

It is of vital importance that the particular signs of this condition should not pass unrecognized. Most ominous and most frequently misconstrued is a complaint of bleeding from a mucous surface.

Further data concerning the present series of cases are given in Table I.

TABLE I.—*Analysis of Series*

Duration of employment at work in contact with T.N.T.

1 month	3 cases	2 died	1 recovered
1–3 months	4 „	2 „	2 „
3–12 „	10 „	5 „	5 „
1–2 years	6 „	4 „	2 „
Over 2 years	4 „	2 „	2 „

Interval between last exposure to T.N.T. and start of illness

Nil: fell sick while working	17 cases
Less than 1 month	6 „
1–3 months	2 „
9 „	1 case
18 „	1 „

Duration of illness

	To date of death	To date of resuming work
9 days	1	—
2–4 weeks	3	—
1–3 months	7	3
3 months to 1 year	4	7
1–2 years	—	2
	15	12

Ultimate cause of death

Intractable recurring haemorrhages	5 cases
Thrombocytopenic purpura	3 „
Agranulocytosis	3 „
Anaemia chiefly affecting the red cells	1 case
Brain haemorrhages	2 cases
Pulmonary embolism	1 case
	15

A purpuric haemorrhage is often the first sign noticed by the worker. In the 15 fatal cases which occurred in the United Kingdom since January, 1940, the first signs or symptoms complained of by the worker, and sometimes the only symptoms appreciated until the terminal phase of the illness, were as follows:—(1) Haemorrhage from a mucous surface (eight cases): epistaxis, three cases (one also had bleeding gums); bleeding from gums, six cases (five were bleeding also from other sites); bleeding from uterus, three cases (also bleeding from the gums). (2) Subcutaneous capillary haemorrhages (five cases), described as "black spots," bruises, or petechiae.

In T.N.T.-workers the sign of *pallor* should never be disregarded. Any degree of pallor calls for an estimation of the haemoglobin, and if this be reduced to 80% a full differential blood count should be done. It is astonishing to what a degree of anaemia the blood may fall with no sign other than pallor.

The following findings should *ensure the temporary removal of the worker from contact with T.N.T.*: haemoglobin reading of 70% or less; white blood cells, 10,000 per c.mm. or more; lymphocytes, over 35% of the white blood cells. Monocytosis and reticulocytosis should not be disregarded.

Case Histories

Five women consulted their doctors on account of black spots or bruises on their bodies or limbs. The history of one of these is given in detail below.

Case 2

A married woman aged 24 entered a factory on July 1, 1942, and worked in and out of contact with T.N.T. until the end of 1944; perhaps 18 months in contact and 12 months in non-contact work. Before leaving the factory, on April 28, 1945, she worked part-time for 18 days, filling bombs with T.N.T. In September she began to feel short of breath. In January, 1946,

she had petechial spots on her arms, legs, and chest, and some bleeding from her gums. She consulted her doctor, but her condition was not recognized. In June she had conjunctival haemorrhages. On August 19 she was admitted to hospital. A blood count showed: red cells, 850,000 per c.mm.; haemoglobin, 21%; colour index, 1.2; white cells, 2,000 per c.mm. (polymorphonuclear cells 23.5%, lymphocytes 75%, monocytes 1.5%); platelets, 10,000 per c.mm.; reticulocytes, 0.9%. Average diameter of the red cells, 7.65 μ; anisocytosis, some macrocytosis, slight polychromasia. She was given 11 pints (6.2 litres) of packed cells by transfusion and also received doses of "anahaemin," "benerva," pyridoxine, ascorbic acid, and "adexolin," "examen," and proteolysed liver.

On September 26 the blood showed: red cells, 3,700,000; haemoglobin, 79%; colour index, 1; white cells, 3,200 (neutrophils 42%, lymphocytes 52%, monocytes 4%, eosinophils 2%). Her heart was enlarged, the apex beat was in the nipple line and sixth intercostal space; the liver and spleen were just palpable; her gums were friable and bleeding easily, there were haemorrhages in the palate; she had had one attack of haematuria. She was discharged from hospital on October 1, but was readmitted on November 8, her condition having deteriorated. On November 21 the blood showed: red cells, 1,800,000; haemoglobin, 31%; colour index, 0.86; reticulocytes only 0.5%. Death occurred on December 26, 1946, one year and eight months after her last contact with T.N.T.

Necropsy.—Right-sided subdural haemorrhage. Pleural and pericardial effusions. Heart: petechiae in endocardium and in muscle. Liver: 2 lb. 14 oz. (1.3 kg.), showed traces of free iron. Haemorrhage in corpus luteum and in uterus. Marrow: of the sternum, good colour and consistency; of the femur, fatty degeneration. Cause of death: aplastic anaemia due to T.N.T. absorption.

In six cases epistaxis and/or bleeding from the gums was the notable symptom. Among these was the following startling case.

Case 9

This chemist, a powerfully built, well-nourished young man aged 19, joined the factory on July 8, 1940, and was employed mainly on analysis of T.N.T. samples in the laboratory, where only small quantities are handled. About once in every two months he did a three-weeks shift in the packing-houses. His duties there involved taking samples per batch from the flaking machine, an operation requiring not more than 15 seconds in possible close contact with T.N.T. dust on each occasion, the rest of his time being spent in checking the markings and general condition of the packing-cases. He never complained of feeling unwell or that the T.N.T. was affecting him in any way. Many chemists were similarly employed without receiving any appreciable harm. At the end of eight months, on March 9, 1941, he went down with influenza. On the fourth day of his illness the factory medical officer was urgently summoned and found him *in extremis*, owing to primary anaemia of unknown origin.

He was at once admitted to hospital, where he gave the history that for three months he had felt easily tired and short of breath, that his nose had been bleeding frequently, and that he was constipated. On March 12 the blood count showed: red cells, 1,380,000 per c.mm.; haemoglobin, 28%; colour index, 1.01; white cells, 1,200 per c.mm. Blood transfusions were started and daily injections of "hepatex." He received also vitamins B and C and intramuscular calcium and "kapilon." On March 26, having had 3 pints (1.7 litres) of blood altogether, his condition had improved, but haemorrhages were found in both retinae. By April 3 he was able to leave his bed. Repeated transfusions had by April 16 brought his red cells up to 4,160,000; haemoglobin, 50%; colour index, 0.71. Agranulocytosis, however, was extreme, the polymorphonuclear cells being only 7%, lymphocytes 83%. On May 10 he was improving; there had been no epistaxis for two weeks. He had been given physical exercise and ultra-violet baths. Almost at once, however, the haemorrhagic phase of his illness set in, the bleeding from the nose and gums becoming uncontrollable. On May 14 the blood showed: red cells, 1,370,000; white cells, 1,500. No platelets could be found. Pentnucleotide injections were given daily from May 16 to 21. He was now covered with purpuric spots from head to foot. A histamine test meal showed achlorhydria before and after the administration of histamine. A van den Bergh test was negative. He received in all some 22 pints (12.5 litres) of blood by transfusion, but died from platelet deficiency on May 31, 1941, eleven and a half weeks from the start of his illness.

Necropsy.—There were widespread petechiae and ecchymoses. The liver seemed healthy but had a rusty look, suggesting haemosiderosis. The mesenteric glands were somewhat enlarged. Marrow: in the ribs, red; in the lumbar vertebrae, more scanty, but red; in the femur, entirely yellow and fatty. Cause of death: aplastic anaemia due to T.N.T.

Another patient, whose illness began with bleeding from gums, recovered after numerous blood transfusions.

Case 12

A woman aged 28 entered a factory on March 13, 1941. She was in and out of contact with T.N.T. until the first week of January, 1942, except for three weeks in October, 1941, when she was given non-contact work because she complained of fatigue, shortness of breath, and poor appetite; at the end of three weeks she felt perfectly well and returned to contact work. On January 1, 1942, she stayed at home on sick leave. On January 26 she was admitted to hospital. There she gave a history that her gums had been bleeding for the past month; that she had had one attack of vomiting; that for three months she had been lacking in energy, and this was getting worse; that if she hurried she got palpitations and a feeling of breathlessness; that two months previously she had a heavy "period." On January 28 a blood count showed: red cells, 850,000 per c.mm.; haemoglobin, 20%; colour index, 1.25; average diameter of red cells, 7.8 μ; white cells, 3,800 per c.mm. (neutrophils 57%, lymphocytes 41%, monocytes 2%); anisocytosis, macrocytosis; cells well stained, no immature whites seen.

On February 3 she was found to have retinal haemorrhages. The icterus index was 10 units, the van den Bergh reaction negative, Webster's test negative. Three days later the red cells had dropped to 730,000; haemoglobin, 17%; colour index, 1; white cells, 5,100 (neutrophils 43.5%, lymphocytes 51%, monocytes 3.5%, eosinophils 1.5%, basophils 0.5%). The marrow, by sternal puncture, showed: polymorphonuclears, 16%; preleucocytes, 18%; myelocytes, 34%; primary erythroblasts, 2%; secondary erythroblasts, 4%; normoblasts, 1%; lymphocytes, 25%.

Comment by Dr. C. V. Harrison: "The blood picture shows a very severe normocytic anaemia. The marrow picture indicates a severe depression of erythroblastic haemopoiesis. The appearance of the case as a whole suggests an aplastic anaemia, particularly affecting the red cells."

The clinical note at this time states: "Feels fine. Looks terrible." Next day the patient had a uterine haemorrhage, and a blood transfusion produced a severe rigor. Fresh haemorrhages appeared in the retinae. Two further blood transfusions were helpful. She was given another 11 pints (6.2 litres) of blood (on five occasions), and was allowed to go home on March 23 to attend every second day for liver injections and to have a weekly blood count. At this time her red cells numbered 4,800,000; haemoglobin, 76%; colour index, 0.8. On May 14 her blood had dropped again to: red cells, 1,800,000; haemoglobin, 38%; colour index, 1.06. She was readmitted to hospital, given three more transfusions, and sent home again on June 20, to attend as before.

On February 5, 1943, a blood count showed: red cells, 4,210,000; haemoglobin, 90%; colour index, 1; white cells, 5,200 (polymorphonuclear 65%, lymphocytes 32%, monocytes 1%, eosinophils 1%, basophils 1%); red cells normal in size and staining. On March 27, 1945, she was well. Blood count: red cells, 5,024,000; haemoglobin, 100%; colour index, 1.0; white cells, 10,000 per c.mm.; red cells normal in size, shape, and staining, no immature reds seen. On May 8, 1946, the blood showed: red cells, 4,000,000; haemoglobin, 85%; colour index, 1.06. She then attended fortnightly for injections of liver and was given iron by mouth. On August 6 a final note says: "Recovered and well." During her illness, in addition to the transfusions, she had received: ferri et ammon. cit., "neohepatex," vitamin C, "campolon," anahaemin, "jectemia," and "betaxan."

Another case of the series was marked by severe uterine haemorrhage.

Case 13

A woman aged 27 entered the factory on February 5, 1942. There was no history of previous illness. She worked in contact with T.N.T. for nine and a half months, never missing a day's work except once when she missed the bus. She attended the routine inspections regularly, never complained, and was recorded as fit. On November 22 she stayed at home, her doctor's certificate stating: "colic"; and a week later, "anaemia and debility." On December 2 she was admitted to hospital on account of uterine haemorrhage, so severe that abortion was suspected. The uterus was explored and emptied—of blood clot only. A blood count showed: red cells, 630,000 per c.mm.; haemoglobin, 12.5%; colour index, 1.0; mean corpuscular

volume, 95 μ^3; white cells, 3,000 per c.mm. (polymorphonuclears 62%, lymphocytes 31%); bleeding-time increased, but not coagulation time. A sternal puncture was done, but the findings were inconclusive. Treatment with liver and iron had no effect. She was given repeated transfusions, but her temperature rose steadily, and she died on January 2, 1943.

Necropsy.—Extreme pallor. Marrow of sternum, femur, and one rib was uniformly yellow except for a faint pinkish colour in the femur. Uterus small and full of clot. Other organs normal except for pallor. Cause of death: aplastic anaemia due to T.N.T. The factory was not informed of the illness until after the post-mortem examination had been made.

The history of the first known case in the United Kingdom of recovery from aplastic anaemia due to T.N.T. was as follows:

Case 14

A married woman aged 36, six children, entered a factory early in August, 1940. She worked for three weeks out of contact, for three weeks in light contact, on filled shells, and then in full contact in the shifting-house. On November 18, after about nine weeks in contact with T.N.T. as shift-house attendant, she reported to the factory medical officer on account of dizziness and weakness, loss of appetite, and loss of weight; she complained also of vomiting and of xiphisternal pain. Her complexion was very sallow, with a suggestion of jaundice; she had icterus of the sclerotics and ulcers in the mouth. The liver seemed smaller than normal, the urine contained bile and gave a positive Webster reaction. She was admitted to the Cardiff Royal Infirmary the same day, under the care of Professor A. M. Kennedy, to whom I am much indebted for the use of his personal notes. On admission she confirmed the history given above, adding that she had some shortness of breath and palpitation, and that her urine had become dark in colour, "like strong tea"; she had not felt well for about a month and had the constant bitter taste of T.N.T. in her mouth. She had had amenorrhoea since February, 1940. Her weight was 6 st. 3¼ lb. (39.6 kg.).

Examination showed a very thin woman, with ashen-grey pallor of lips, pale sallow complexion, but no jaundice; a bald tongue with small ulcers beneath it, and some abdominal tenderness. The liver and spleen were within normal limits, the stools normal in colour. Van den Bergh: negative direct but weak positive indirect reaction; icterus index, 5 units; Kahn negative; no methaemoglobin found. A blood count showed: red cells, 2,620,000 per c.mm.; haemoglobin, 70%; colour index, 1.3; white cells, 3,200 per c.mm. (polymorphonuclears 44%, lymphocytes 50%, monocytes 5%, myelocytes 1%); the cells were toxic, lymphocytes and polymorphonuclears containing dark granules; numerous megalocytes and few microcytes, no poikilocytes, no polychromasia; a very occasional reticulocyte on searching; platelets, 52,000 per c.mm. Urine: Webster reaction positive on admission and for the next nine days. Porphyrinuria was present (++) throughout her stay in hospital and then gradually lessened, to disappear at the 27th week from the start of her illness. A very faint trace of albumin during her last week in hospital. Fractional test meal showed the acid content of her stomach to be low; no free HCl present.

Progress.—On admission to hospital she was gravely ill. During her stay of 14 weeks, from November, 1940, to February 21, 1941, her general symptoms soon abated, though her blood improved but slowly. Just before leaving hospital the blood count was almost normal; she looked and felt very well and had put on over 3 st. (19 kg.) in weight. Blood examination: red cells, 4,560,000; haemoglobin, 92%; colour index, 1.01; white cells, 8,200; platelets, 228,000. After leaving hospital she attended at first weekly, and then fortnightly, for 21 weeks, until her confinement in November, 1941. This confinement was normal, and she nursed the baby for a year without any setback to her health. She again attended from time to time until the summer of 1943, when she was once more advanced in pregnancy, expecting her eighth child.

Treatment.—Neohepatex, either 2 or 4 ml. intramuscularly, was given three times a week, for one month, total 40 ml.; then, anahaemin, 2 ml. intramuscularly, three times a week for five weeks, then daily for one week; then, ventriculin, 30 g. daily by mouth, from February 4 to the end of October, 1941, when she entered a maternity home. On leaving the home, on November 18, she again took ventriculin until just before Christmas. For one month during her pregnancy she received ferri et ammon. cit., 30 gr. (2 g.) t.d.s., and again while in the maternity home. While in the home she was also given campolon.

Two women developed aplastic anaemia following T.N.T. jaundice. The case history of the first is given below.

Case 15

A woman aged 26 who had always enjoyed good health entered a factory on October 19, 1940. She worked in contact with T.N.T. until November 14 (just under four weeks). She then sprained her wrist and was given light non-contact work for one month. On December 16, on attending the factory surgery because of her wrist, she was seen to be jaundiced, her liver was enlarged, there was bile in her urine, and she had some abdominal tenderness and pain. She was admitted the same day to the Cardiff Royal Infirmary under the care of Professor A. M. Kennedy, to whom I am indebted for the use of his personal notes.

On admission she said she had felt quite well until the beginning of December, when she had been on night shift for about a week. She then began to feel sick and averse to any food. She had no vomiting, no headache, no dizziness. She began to have two or three loose greyish motions a day, and epigastric pain; the urine darkened in colour and her eyes became slightly yellow. Her menstrual period, due on December 11, did not occur.

Examination showed she was thin, weighing 6 st. 11¼ lb. (43.3 kg.), with slight general icterus, tongue moist, no ulceration in mouth, lips slightly cyanosed. Heart: first aortic sound weak. Nothing else amiss in chest. The liver could be felt 1 in. (2.5 cm.) below the costal margin, in nipple line. Tenderness was present in epigastrium and over ascending and descending colon. The van den Bergh reaction was biphasic; icterus index, 35 units; Kahn negative; no methaemoglobin found. During the next three weeks her general condition steadily improved; by January 21, 1941, she was looking well and feeling very well. She had put on weight, the jaundice was practically gone, and no cyanosis was to be seen. She was enjoying her food; weight, 7 st. 6 lb. (47.2 kg.).

On January 28 she felt all right, but her skin was pale and unhealthy-looking and she was perspiring freely. The liver had increased in size until the margin could be felt halfway between the ensiform and the umbilicus. The red blood cells were becoming megalocytic. On January 31 the terminal phase of her illness set in: her temperature rose high, her mouth showed gingivitis with necrotic patches around the bases of the teeth, there were submucous haemorrhages on the lower lip and tip of tongue, the tongue was thickly coated and the pharynx reddened. Soon the gums were bleeding freely and there was subconjunctival haemorrhage. She received 1 pint (570 ml.) of blood by transfusion without relief, and on February 5 she died. The blood counts are shown in Table II. No megaloblasts seen; practically no poikilocytosis, no polychromatophilia. Variation in size was the feature of the film, but the variation was in an upward direction. An occasional cell was about 6 μ in diameter, many were 10 μ and up to 12.5 μ, and some were fully 15 μ. Nucleated red cells were not seen.

TABLE II.

Date	Red Cells per c.mm.	Hb %	C.I.	White Cells per c.mm.	Polymorphs %	Lymphocytes %	Monocytes %	Eosinophils %	Premyelocytes %	Platelets per c.mm.
17/12/40	5,100,000	92	0·90	5,000	70	22	7	1	—	132,000
24/12/40	5,000,000	98	0·98	8,000	67	28	4	1	—	140,000
31/12/40	4,900,000	96	0·98	7,200	67	28	3	1	2	147,000
7/1/41	4,320,000	92	1·07	5,200	52	43	2	1	2	129,600
14/1/41	4,060,000	90	1·12	4,400	34	59	4	1	2	81,200
21/1/41	3,650,000	90	1·23	3,200	31	63	4	1	1	51,100
28/1/41	3,070,000	74	1·23	4,400	7	87	5	1		30,700
3/2/41	2,010,000	50	1·25	2,000	0	84	4	0	7	8,040

On January 28 lymphoblasts were present, and on February 3 Türk's irritation cells (5%).

Urine.—Webster reaction negative throughout. For the first three weeks there was a very faint trace of albumin. For two and a half weeks bile pigments were present, and then urobilinogen for five days. No urobilin was found. Porphyrinuria was present—a heavy deposit for the first three weeks, then variable. An ether-soluble deposit was present for 18 days from the start of the fourth week, reappearing before death.

Necropsy.—Necrosis of the liver. Widespread purpuric haemorrhages in the skin and mucous and serous membranes. Ulceration of tongue. Congestion of lungs, with oedema of lower lobes and partial collapse of lower lobe of left lung.

"Dust cells" more numerous than normal. The heart showed numerous haemorrhages in the pericardium and in the muscle; the aorta was small, with some fibrosis and stenosis at the point of entry of the ductus arteriosus. The femur contained red gelatinous marrow in the upper half of the shaft. The lymph nodes were not greatly enlarged, they contained much brown pigment, mostly in phagocytic cells.

Six cases were admitted to the Royal Infirmary, Salford, under the care of Professor R. E. Lane, to whom I am indebted for the use of his reports. All these patients recovered. The histories of two were as follows:

Case 19

A young woman aged 21 entered a factory on March 4, 1942, and worked for three months in contact with T.N.T. On June 7 she was found to be deeply jaundiced. She gave a history that two weeks previously she had caught a bad cold and that for the past week she had had pain in her stomach, with sickness and jaundice. On admission to Salford Royal Infirmary next day she was deeply jaundiced, the van den Bergh test gave a positive direct reaction, the serum bilirubin amounting to 29 mg. per 100 ml. Bilirubin was present in the urine and there was a slight excess of urobilin. A laevulose-tolerance test was slightly abnormal (low starting and finishing figures). A blood count showed: red cells, 4,500,000 per c.mm.; colour index, 1.15; mean diameter of red cells, 8 μ. She was discharged home on July 24, her serum bilirubin still 5 mg. per 100 ml., still jaundiced, haemoglobin 76%. She had gained in weight and was feeling well. One month later (August 27) she reported at the factory, feeling very tired. The conjunctivae were still jaundiced, her lips and mucous membranes very pale, her feet swelling. She was sent to hospital by ambulance. Blood showed: red cells, 1,040,000; haemoglobin, 28%; colour index, 1.4; mean diameter of red cells, 7.4 μ; white cells, 3,000 (polymorphonuclears, 28%); platelets, 450,000 per c.mm. She was immediately given 3 pints (1.7 litres) of whole blood, then treated with rest, iron, full diet with added vitamins. Her blood deteriorated, and she again received tranfusion, and was allowed to go home on October 7. On November 14 she was readmitted to hospital. Blood showed: red cells, 1,900,000; haemoglobin, 60%; mean diameter of red cells, 7.8 μ; colour index, 1.6; white cells, 5,600 (polymorphonuclears 28%). Sternal puncture found marrow which was active and cellular, but with inversion of the erythromyeloid ratio; the red cells were extremely large. Once more she was transfused, and sent home for a month. From this time she steadily recovered and was able to return to non-contact work on January 11, 1943. On December 1, 1943, a blood count showed: red cells, 4,400,000; haemoglobin, 104%; colour index, 1.18; mean diameter, 7.6 μ; white cells, 5,900 (polymorphonuclears 50%). On November 26, 1946, her doctor wrote that she was in a state of advanced pregnancy and "looking as fit as can be."

In the second case illness started 18 months after a very short period of contact with T.N.T.

Case 24

A man aged 46 entered a factory on December 28, 1939, and worked in full contact with T.N.T. for only five weeks, from July 6 to August 8, 1940. He was then taken permanently out of contact. He complained that he was short of breath, had a poor appetite, and felt lifeless. He was cyanosed and pale. His symptoms subsided, and he remained well until February 7, 1942, when he reported to his own doctor on account of neuritis. His pallor was noticed, but he said he felt fine. On March 19 he was admitted to hospital in a state of aplastic anaemia. He was pale but cheerful; there was no wasting, and no symptoms except that he felt short of breath on exertion. A blood count showed: red cells, 1,700,000 per c.mm.; haemoglobin, 35%; colour index, 1; mean diameter, 7.5 μ; white cells, 4,800 per c.mm. (polymorphonuclears 51%). The van den Bergh reaction was negative; serum bilirubin, 0.6 mg. per 100 ml. Sternal puncture showed a markedly cellular marrow, lymphocytes predominating, with a few normoblasts and myelocytes. He was treated with repeated transfusions of blood, up to 4 pints (2.3 litres) at a time, until October, 1943. By this time he had received 37 pints (21 litres) of whole blood, and he gradually recovered. On January 26, 1944, a blood count showed: red cells, 2,500,000; haemoglobin, 66%; colour index, 1.3; mean diameter, 8 μ; white cells, 6,200 (polymorphonuclears 52%). Further treatment with vitamins B and C was given and his butcher was asked to provide him whenever possible with liver, tripe, and hearts. In July, 1944, he started light work, out of contact.

Treatment

Early and complete removal from contact with T.N.T. is the first essential. Blood transfusions were given in 19 of the 24 cases of aplastic anaemia. Four of these patients were given packed cells; for the other 15 whole blood was used. The dosage varied from 500 ml. to 4 pints (2.3 litres). The largest total quantities given were: 46 pints (26.1 litres) over a period of 12 months to a man who eventually recovered; 37 pints (21 litres) over a period of 18 months, 23 pints (13 litres) over 3½ months, both patients surviving; 22 pints (12.5 litres) over 11½ weeks to a man who died.

Liver preparations, iron, and vitamins B, C, K, and P were all freely given. Pentnucleotide was prescribed in four cases.

Of the four patients who did not receive transfusion three recovered, one died without admission to hospital. In one case the hospital records have been destroyed.

It is clear that treatment by blood transfusion needs to be adjusted with great care. It is generally agreed that no attempt should be made to restore the blood cell count or the haemoglobin content to normal levels, for the haemopoietic function of the bone marrow may be depressed by such massive donations. The object must be to maintain a blood level sufficient to support life, with a safety margin, until the haemopoietic tissues recover from their intoxication and resume their proper duty of supplying cells to the blood. Bomford and Rhoads (1941) suggest, further, that an increased rate of haemolysis may follow excessive transfusion; it is indeed surprising how quickly, after transfusion, the blood can revert to its former poor condition. These authors state that patients who have been ill for some time are usually comfortable in bed with a Hb level of about 30%; patients up and about usually require to be kept at a slightly higher level. The method they recommend as ideal is to give not more than 500 ml. of blood at a time—whole, unaltered, fresh blood from a donor of identical group—and to give rapidly by a multiple syringe method. Post-transfusion reactions, they say, are thus reduced to a minimum.

This has not been precisely our experience. Professor R. E. Lane, whose six successful cases are in this series, made it his practice to give larger quantities of blood, at longer intervals. The initial transfusion was of 2 or 3 pints (1.1 or 1.7 litres) and, with convalescence, the patient was filled up with 3 or even 4 pints (1.7 or 2.3 litres) at a time and then sent home for a month or longer, to return for examination and repeat treatment if the blood level had not been naturally maintained. A haemoglobin level of not more than 60% was found to be adequate. While the blood level was thus maintained, restoration of haemopoiesis was encouraged by the administration of liver, iron, vitamins B, C, and K, and, in one case without transfusion, ventriculin (Kennedy and Ingham, 1942).

Eddy (1944) emphasizes the importance of giving fresh blood, not more than 24 hours old, to secure the value of the short-lived white cells and platelets.

It was inevitable that transfusion reactions should have appeared in several of the cases, for they occurred from 9 to 13 years ago, when the Rh factor (discovered in 1940) was not yet fully known, and any blood transfusion was somewhat of a venture. A determination of the Landsteiner group (ABO) was usually, but not necessarily always, followed by bedside matching, and reactions were not infrequent. One woman, group A, was given 5 pints (2.7 litres) of blood, and for this purpose 16 donors were brought in, 14 of them of group A and two of group O. She matched only with the two group O bloods and with three of group A. Difficulty was experienced at times in finding a suitable vein, as not all house-physicians were expert in the technique. Details are not recorded in most cases, but in some the blood was given by slow drip. To illustrate the difficulties it may be stated that the diagnosis "toxic rash" on a sick certificate brought the factory medical officer out post-haste to see an employee who had been admitted to hospital. The patient was found to be in a state of grave

anaemia, but he had to be removed to another hospital for treatment, because never in the history of the first hospital had a blood transfusion been given.

Summary

Twenty-four cases of aplastic anaemia caused by the absorption of trinitrotoluene (15 being fatal) are recorded. Of the nine patients who recovered, six were treated by multiple blood transfusions with administration of liver, iron, and vitamins; three received liver, iron, and vitamin therapy, but no blood transfusion; one of these three also received ventriculin.

Analysis is made of these 24 cases and of three cases of early toxic anaemia due to the same cause. The insidious onset of aplastic anaemia sets a difficult problem.

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An interim statement has been made to the Minister of Health, Mr. E. A. NUGAWELA, by Mr. DONALD BARLOW and Professor ROBERT NEUBAUER, of the World Health Organization, and Professor JOHN CROFTON, of Edinburgh, on the progress made by the Ceylon Government in implementing Mr. Barlow's recommendations, made in 1952, for reorganizing the campaign against tuberculosis. On returning to Ceylon, states the report, Mr. Barlow was forcibly struck by the many improvements which had occurred. Great strides had been made in both prevention and cure. The team felt that there was still a long way to go, but the Government had attacked the problem with vigour and determination. No Government could have been more alert to its responsibilities. The report draws attention to the enthusiasm of those taking part in the scheme, noting that the hopelessness on the faces of the patients in the grossly overcrowded and ill-equipped wards had given place to hope, cheerfulness, and expectation of recovery. *X*-ray facilities are being increased, and a start has been made in the provision of pathological and bacteriological services. Since 1952 the mortality from diagnosed tuberculosis has been halved. This is attributed partly to the provision by the Government of large funds for the purchase of modern drugs. The training of doctors and nurses still presents a big problem. A fair number have taken advantage of the Colombo Plan Scheme of training in England, but at least one more fully staffed and equipped medical school is required in Ceylon.

THE EFFECT OF INSULIN ON NITROGEN RETENTION IN THE HYPOPHYSECTOMIZED RAT

BY

R. T. B. LAWRENCE, B.Sc.(Med.)
Research Assistant, Department of Physiology

JAMES M. SALTER, M.A.
Research Associate, Department of Physiology

AND

CHARLES H. BEST, M.D., F.R.S.
Director, Department of Physiology, and Banting and Best Department of Medical Research

University of Toronto, Toronto, Canada

It has been reported from this laboratory that exogenous insulin promotes growth in hypophysectomized rats.[1,2] These animals gain weight owing to increases in protein, fat, and water. The observed increases in body protein stimulated us to study in some detail the effect of insulin on nitrogen retention.

Procedure

Male rats with an average body weight of 119 g. which had been hypophysectomized 14 days previously were used in all experiments. The animals were maintained in a constant-temperature room at 28° C. In Experiment A the daily nitrogen balances of six untreated hypophysectomized rats were determined for a 12-day period. In Experiment B hypophysectomized rats were divided into one control group of 12 animals and one experimental group of eight animals. Nitrogen-balance studies were not performed on the controls, but a good indication of the balance maintained by these animals during the experimental period was secured by determining changes in the nitrogen content of their carcasses. This observation was made by sacrificing six of the rats on the initial day of the experiment and comparing their average total body nitrogen with a similar value obtained from the remaining six controls sacrificed on the last day of the experiment.

The daily nitrogen balance of each of the eight rats in the experimental group was determined for (*a*) an initial period of three days before insulin was administered; (*b*) an intermediate period of seven days during which each rat received one daily injection of increasing amounts of protamine zinc insulin; and (*c*) a four-day period following the cessation of insulin treatment. These rats were sacrificed with surviving members of the control group on the fourteenth day. Total body nitrogen determinations were made on each carcass. The nitrogen balance was regarded as the difference between nitrogen ingested and nitrogen excreted in the faeces and urine.

The food mixture consisted of the following ingredients: water, 1,200 ml.; "Chum" dog food, 890 g.; dried white bread crumbs, 335 g.; powdered skim-milk, 145 g. The glucose was dissolved in the water and this solution used to reconstitute the powdered milk. The remaining constituents were thoroughly mixed in and the whole was homogenized in a Waring blender.

Dry-weight determinations were made on nine samples of the diet. The nitrogen contents of these dried samples were determined. The results agreed very closely and showed that the diet was well homogenized.

All rats ate *ad libitum*. To avoid errors due to evaporation, the amount of food given each rat daily was calculated in terms of its dry weight. The food remaining from the previous day was removed and dried to constant weight. The dry weight of the food eaten was then determined and

the nitrogen intake calculated. Errors in estimations of nitrogen intake were minimized by eliminating rats that showed a tendency to scatter their food.

Each rat was placed in a cylindrical wire metabolism cage suspended over a large funnel. A fine wire mesh prevented the faeces from passing into the funnel below. The stools were carefully collected from the bottom of the cage once daily. Each collection of stools was digested in sulphuric acid with a selenium catalyst. The digest was then diluted and nitrogen determinations were made on aliquots.

A thin layer of glass wool placed in the apex of the funnel prevented hair and scales from passing into the vessel in which the urine was collected under toluene. The cage floor, funnel, and glass wool were washed down thoroughly with distilled water at each urine collection. The total volume of the combined urine and washings was measured and an aliquot retained for nitrogen determinations.

Total body fat was determined on the carcasses of animals used in this investigation in connexion with other work. Therefore the total body nitrogen content of each rat was determined from the fat-free residue in the following way. The whole defatted carcass was digested for 10 hours in boiling sulphuric acid containing selenium catalyst mixture. The digest was then diluted and aliquots of this were redigested before their nitrogen contents were determined. All nitrogen determinations were carried out in duplicate by the micro-Kjeldahl technique.

TABLE I.—*Average Daily Nitrogen Balance of Six Untreated Hypophysectomized Rats*

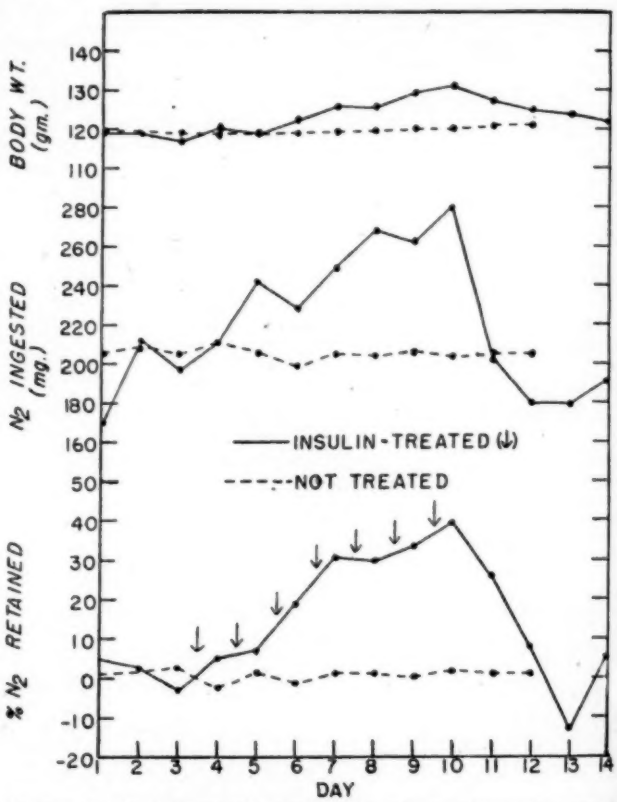
Day	Av. Wt. (g.)	Food Mg.-N_2	Urine Mg.-N_2	Faeces Mg.-N_2	Balance Mg.-N_2	% N_2 Retained	% N_2 Urine	% N_2 Faeces
1	119·0	205·1	174·3	28·8	+2·0	0·97	84·98	14·04
2	118·8	209·0	175·3	29·7	+4·0	1·91	83·87	14·21
3	119·1	205·1	172·5	26·9	+5·7	2·78	84·10	13·12
4	118·8	210·1	185·6	29·3	−4·8	−2·28	88·33	13·95
5	119·1	206·5	176·0	27·7	+2·8	1·36	85·23	13·41
6	119·7	199·6	175·3	26·8	−2·5	−1·25	87·82	13·43
7	119·6	205·5	172·1	30·0	+3·4	1·65	83·74	14·60
8	119·6	204·3	172·0	29·3	+3·0	1·47	84·19	14·34
9	120·0	206·8	177·8	29·3	−0·3	−0·15	85·97	14·17
10	120·2	203·0	170·6	28·6	+3·8	1·87	84·03	14·09
11	120·8	204·6	173·5	28·1	+3·0	1·47	84·79	13·73
12	121·0	204·3	172·8	28·5	+3·0	1·47	84·58	13·95

TABLE II.—*Average Daily Nitrogen Balance of Eight Insulin-treated Hypophysectomized Rats*

Day	Insulin Units	Food Mg.-N_2	Urine Mg.-N_2	Faeces Mg.-N_2	Balance Mg.-N_2	% N_2 Retained	% N_2 Urine	% N_2 Faeces
1	0	169·2	143·9	18·0	+7·3	+4·31	85·05	10·64
2	0	212·6	170·8	35·9	+5·9	+2·77	80·34	16·89
3	0	197·2	175·4	29·3	−7·5	−3·80	88·95	14·86
4	0·5	211·2	163·8	37·3	+10·1	4·78	77·56	17·66
5	1·0	240·8	187·9	36·2	+16·7	6·94	78·03	15·03
6	1·0	228·1	149·9	34·0	+44·2	19·38	65·71	14·91
7	1·4	249·3	133·5	39·6	+76·2	30·56	53·55	15·88
8	1·8	268·6	152·2	36·6	+79·8	29·70	56·66	13·63
9	2·4	262·7	136·6	38·8	+87·3	33·23	52·00	14·77
10	3·0	280·4	130·9	39·9	+109·6	39·09	46·68	14·23
11	0	203·4	110·1	40·1	+53·2	26·15	54·13	19·71
12	0	180·0	131·5	33·5	+15·0	+8·33	73·05	18·61
13	0	181·6	172·0	33·1	−23·5	−12·94	94·71	18·23
14	0	190·2	154·8	25·6	+9·8	5·15	81·39	11·46

Results

The results of this investigation are presented in Tables I, II, and III and the Chart. It was found in Experiment A that under the conditions of this investigation untreated hypophysectomized rats remain in nitrogen equilibrium (Table I and Chart). This observation was supported by the results of Experiment B. The untreated controls remained in nitrogen equilibrium, since their average total body nitrogen content did not change during the experimental period (Table III). The carcass analysis shows that the nitrogen content of the insulin-treated hypophysectomized rats was greatly increased (Table III). This is in accord with the data obtained from the nitrogen-balance studies carried out on these animals. When insulin was administered to hypophysectomized rats (Chart) there



Changes in the average nitrogen intake, nitrogen retention, and body weight of six untreated hypophysectomized rats and eight insulin-treated hypophysectomized rats. The dose of insulin was 0.5 unit for the first day and 1, 1, 1.4, 1.8, 2.4, and 3 units for the subsequent days.

TABLE III.—*Total Body Nitrogen Contents of Hypophysectomized Rats*

Controls Killed Day 1				Controls Killed Day 14				Insulin-treated Killed Day 14			
Rat No.	Final Fasting Wt. (g.)	Wt. Change (g.)	Total Body N_2 (mg.)	Rat No.	Final Fasting Wt. (g.)	Wt. Change (g.)	Total Body N_2 (mg.)	Rat No.	Final Fasting Wt. (g.)	Wt.* Change (g.)	Total Body N_2 (mg.)
9	110·9	0	3,235	15	115·0	4·0	3,204	1	127·6	9·0	3,829
10	117·4	0	3,316	16	118·2	1·5	3,288	2	113·0	7·9	3,602
11	106·2	0	3,186	17	117·3	5·8	3,250	3	118·9	1·1	3,683
12	114·2	0	3,282	18	121·0	4·0	3,300	4	126·8	9·8	3,950
13	118·0	0	3,344	19	132·0	4·9	3,461	5	118·0	7·2	3,800
14	123·3	0	3,475	20	125·9	6·9	3,365	6	118·0	1·9	3,807
								7	117·5	4·1	3,737
								8	109·8	−3·0	3,713
Average	115		3,306		121·6	4·5	3,311		118·7	4·7	3,765

* During the last four days of the experiment rats in this group lost much of the weight they had gained (see Chart and Discussion).

was a marked increase in the absolute amount and percentage of nitrogen retained. The increase in food intake and in body weight is apparent. The changes in the percentage of nitrogen retained were due to changes in the proportion of ingested nitrogen excreted in the urine (Table II), whereas the percentage of the ingested nitrogen that was excreted in the faeces remained relatively constant. It is apparent (Chart) that nitrogen equilibrium was restored when the insulin injections were stopped. This latter change in nitrogen balance was accompanied by a fall in body weight. The loss of weight was due to the loss of fat or water or of both. No appreciable amount of protein was lost, since the animals did not exhibit a significantly negative nitrogen balance.

Discussion

The hypophysectomized insulin-treated rats were not maintained on a restricted diet, since this preparation is extremely sensitive to the hypoglycaemic action of insulin. The effect of the increased caloric intake has therefore not been defined. MacKay *et al.*[3] have shown that insulin enhances nitrogen retention in intact rats maintained on a restricted diet.

Our data suggest that a linear relationship may exist between insulin dosage and nitrogen retention. This relationship might have been more apparent if it had been possible to prevent compensatory decreases in pancreatic beta-cell activity which undoubtedly occurred. Chaikoff and Forker[4] have shown that in depancreatized dogs the amount of insulin administered is linearly related to the amount of nitrogen retained.

Since Banting, Campbell, and Fletcher[5] first showed that insulin decreases the nitrogen excreted by diabetic patients, abundant evidence has accumulated to indicate that insulin is intimately associated with protein synthesis. It has been shown *in vivo* and *in vitro* that the antidiabetic hormone stimulates the utilization of amino-acids and the synthesis of proteins and inhibits protein catabolism.[6-16] The results of our experiments are in accord with this evidence and they confirm and extend our previous reports.

Summary

The effect of insulin on nitrogen balance in the hypophysectomized rat has been studied. It has been found that under the conditions of this investigation hypophysectomized rats treated with insulin show a marked increase in the absolute amount and in the percentage of nitrogen retained. Over the range studied the percentage of ingested nitrogen retained bore an approximately linear relationship to the amount of insulin given.

The results of these experiments confirm and extend the earlier reports from this laboratory that insulin can function as a growth hormone in the absence of pituitary factors.

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THE USE AND ACTION OF CHLORPROMAZINE IN PSYCHONEUROSES

BY

GERALD GARMANY, M.B., M.R.C.P., D.P.M.
ANTHONY R. MAY, M.B., B.S., D.P.M.

AND

ALECK FOLKSON, M.D., D.P.M.
Department of Psychiatry, Westminster Hospital

Of recent years a number of compounds with specific pharmacodynamic properties have been developed in France from derivatives of th aromatic base phenothiazine. These compounds include promethazine hydrochloride (" phenergan "), diethazine hydrochloride (" diparcol "), ethopropazine hydrochloride (" lysivane "), and promethazine 8-chlorotheophyllinate (" avomine "). Their usefulness lies in their specific antagonism towards naturally occurring histamine, adrenaline, and acetylcholine, and in the central depressant action which they show in varying degrees, the exact mechanism of which is not clearly understood.

A new derivative of phenothiazine—chlorpromazine hydrochloride (3 - chloro - 10-(3'-dimethylaminopropyl)-phenothiazine ; " largactil ")—is now available in this country. Like the others, it was developed in France, and clinical trials there indicated its possibilities in anaesthesia, as an anti-emetic agent, and in the treatment of psychiatric illness.

In the psychiatric field, Sigwald and Bouttier (1953a) claimed that the drug exerted a depressant action on the central and autonomic nervous systems, and that it displayed special properties which they have called " neuroplegic," producing results comparable to those of " frontal lobotomy." The drug has been employed in the treatment of both psychotic and psychoneurotic patients. Sigwald and Bouttier (1953b) published the results in a series of 48 patients, of whom 12 appear to have been cases of psychosis, while the remainder were psychoneurotic.

These investigators state that chlorpromazine nearly always improved the mood of their patients, and led to the disappearance of depression, with the frequent development of some degree of euphoria. Patients are said to have become indifferent to their worries. Anxiety was replaced by a feeling of calm and detachment, and morbid thoughts disappeared. They state furthermore that " the effect on obsessions is often significant, and sometimes remarkable," while there is " a rapid and complete alleviation of fears, scruples, doubts, and phobias." True obsessional states, on the other hand, are said to give poorer results, though the patient is able to overcome his obsessional thoughts more easily.

The results of treatment with chlorpromazine are said to be characterized by a significant percentage of successes, and analysis of their results shows that these were " good " or " very good " in 50 to 60% of each of the psychoneurotic manifestations they investigated.

In view of the encouraging possibilities of chlorpromazine over such a wide field, it was decided to investigate its effect on a series of psychoneurotics comparable to that of Sigwald and Bouttier.

Administration

Our series of cases numbered 29 and all received chlorpromazine by the oral (as opposed to the intramuscular) route, so that we could standardize the results of in- and out-patient treatment.

The scheme of dosage followed was that suggested by the French investigators. Because of the side-effects reported, dosage was at first low, and the patients were kept in bed for three days at the beginning of treatment and thereafter advised to lie supine for half an hour after taking the drug, to counteract any postural hypotension. As our experience increased, however, we were able to dispense with these precautions, and patients are now only advised to rest for 15 minutes in a chair when starting treatment. After a week they are usually able to tolerate therapeutic doses with no special precautions.

We have found that it is better to start with a high dosage of chlorpromazine and increase quickly to the optimum. Patients are now given 25 mg. t.d.s., and this is raised by 25 mg. every other day to a maximum of 75 mg. t.d.s. In many cases the optimum effect is attained with 50 mg. t.d.s.; and no increased benefit was gained by raising the dose above 75 mg. t.d.s. in our series. Chlorpromazine in these amounts is well tolerated over a long period and out-patients are able to continue at work while undergoing treatment.

In the initial phases of our trial we started with smaller doses, and increased to an optimum over a longer period. We found, however, that many patients complained of an increase in tension and an exacerbation of symptoms, and this method of treatment was replaced by that outlined above. It seems that the maximum clinical improvement may be expected in four to six weeks of treatment. Thereafter a maintenance dose of 50–100 mg. daily is necessary. Cessation of treatment has usually led to a recurrence of symptoms, unless psychotherapy has been successfully employed in conjunction with chlorpromazine.

Complications

The side-effects of chlorpromazine are mainly attributable to its action on the autonomic nervous system, and in our series these have not caused much inconvenience. In two cases tachycardia and dryness of the mouth prevented continued treatment, and in one case there was complaint of weakness of the legs for one to two hours after dosage, but this proved to be only transient. Two further patients with hypertension developed tachycardia and a fall in blood pressure of over 40 mm. soon after taking chlorpromazine.

A far more disturbing complication has been the appearance of pyrexia—temperature 101–103° F. (38.3–39.4° C.)—after seven to ten days of treatment. This has occurred in 10% of all cases treated. At the onset of pyrexia these patients had received total amounts of chlorpromazine varying from 550 to 1,200 mg. Symptoms included profuse perspiration, nausea, and epigastric discomfort, while all displayed epigastric and right subcostal tenderness. On stopping chlorpromazine, the pyrexia subsided in 24 to 48 hours in all cases, with complete remission of symptoms. In two cases chlorpromazine was resumed and has been continued now for three months with no further ill effects. In three other cases the urine was found to contain bile salts, and liver-function tests showed abnormal bromsulphthalein retention, though flocculation tests and serum bilirubin were within normal limits. One of these latter cases was given chlorpromazine again on two separate occasions after the bromsulphthalein retention returned to normal, but each time a pyrexia developed within 24 hours, and treatment was discontinued in these three cases.

Nature of Cases

A brief clinical summary of each of the 29 cases follows. We have omitted any description of the personality setting, which did not appear to be correlated with the response to chlorpromazine to any degree further than already emerges from the diagnosis made.

Cases With Mainly Hysterical Features

Case 1.—Female, 63. Chronic hysteria. Main symptoms: paraesthesia of head. Three months' treatment. No improvement.

Case 2.—Male, 37. Reactive depression with hysterical features. Depression, headaches, abdominal discomfort. Eight weeks' treatment. No improvement.

Case 3.—Female, 57. Anxiety state with hysterical features. Abdominal pain, mild tension. Four weeks' treatment. Slight relief of tension. Relief of pain.

Case 4.—Female, 41. Chronic anxiety hysteria. Vomiting, moderate tension. Three months' treatment. Relief of vomiting, slight relief of tension.

Cases With Mainly Phobic Features

Case 5.—Male, 40. Phobic state. "Choking." Four weeks' treatment. Relief of tension; symptoms remain less obtrusive.

Case 6.—Female, 29. Anxiety state with phobic features, panic attacks. Eight weeks' treatment. Considerable relief of tension, panic attacks persist but more easily controlled.

Case 7.—Female, 29. Chronic anxiety state with phobic features. Panic attacks. Six weeks' treatment. Slight relief of tension, no effect on panic attacks.

Case 8.—Male, 31. Chronic anxiety state with phobic features. Pain in back, cancerophobia. Four weeks' treatment. Relief of tension with corresponding improvement in phobia. (Patient himself noted return of symptoms on voluntarily stopping chlorpromazine.)

Case 9.—Female, 34. Chronic obsessional state with marked phobic features. Tension, claustrophobia, agarophobia. Three months' treatment. No improvement.

Case 10.—Male, 42. Chronic anxiety state in an obsessional personality. Embarrassment. Eight weeks' treatment. Slight relief of tension only.

Cases With Mainly Depressive Features

Case 11.—Male, 51. Chronic anxiety depression. Depression, pain in head and abdomen. Four weeks' treatment. Slight relief of tension, symptoms unchanged. (This patient had a prefrontal leucotomy in 1949.)

Case 12.—Male, 63. Chronic depression. Guilt and depression. Six weeks' treatment. No improvement.

Case 13.—Female, 37. Reactive depression. Depression, malaise. Four weeks' treatment. No improvement.

Cases With Mainly Obsessional Features

Case 14.—Male, 51. Chronic anxiety state, with paranoid, obsessional, and hysterical features (a syndrome with poor prognosis). Tension, orbital pain, inability to read. Six weeks' treatment. Relief of tension, obsessions unchanged (fairly good clinical result, not much response to anything but chlorpromazine).

Case 15.—Female, 32. Endogenous depression with obsessional features. Macabre ruminations and severe tension. (Previous E.C.T. with only transient relief.) Eight weeks' treatment. Marked relief of tension, persistence of obsessional thinking, but decrease in associated features.

Case 16.—Female, 45. Chronic anxiety depression with obsessional features. Depression, phobias, panic attacks. (Previous E.C.T. with only transient relief.) Four months' treatment. Slight relief of tension, panic attacks more easily controlled. No improvement in depression or obsessional thinking.

Case 17.—Female, 41. Chronic obsessional state. Depression, phobias, panic attacks. Three months' treatment. Moderate relief of tension, with slight improvement of depression. Phobia and panic attacks unchanged. (E.C.T. combined with chlorpromazine.)

Case 18.—Male, 28. Chronic obsessional state. Smell from body, tension. Four weeks' treatment. Slight relief of tension, no change in obsessional thinking.

Cases With Pain as Main Feature

Case 19.—Female, 61. Chronic depression. Pain in perineum (central, non-psychogenic). Six weeks' treatment. No improvement.

Case 20.—Male, 64. Chronic involutional depression. Pain in perineum (central, non-psychogenic). No relief with E.C.T. Six weeks' treatment. No improvement.

Cases With Tension as Main Feature

Case 21.—Female, 54. Chronic reactive depression. Severe tension and depression. Ten weeks' treatment. Complete relief of tension, with disappearance of depression.

Case 22.—Female, 71. Chronic anxiety state. Severe tension, insomnia, pain in back, indigestion. Eight weeks' treatment. Relief of all symptoms.

Case 23.—Female, 36. Explosive diathesis—tension state. Severe tension, particularly premenstrually, with detonation. Six weeks' treatment (combined with phenytoin sodium). Marked improvement.

Case 24.—Female, 32. Reactive anxiety depression. Severe tension, tremor, irritability. Three weeks' treatment. Marked relief of all symptoms.

Case 25.—Female, 37. Chronic anxiety state with hysterical features. Moderate tension. Six weeks' treatment. Relief of tension.

Case 26.—Female, 28. Chronic anxiety state with phobic features. Moderate tension, indigestion and flatulence. Four weeks' treatment. Complete relief of all symptoms.

Cases of Dysmenorrhoea

Case 27.—Aged 23. Symptoms for six years. No relief with other treatment. Chlorpromazine gives "50% relief."

Case 28.—Aged 20. Symptoms for four years. No relief from analgesics. Chlorpromazine gives "considerable relief."

Case 29.—Aged 20. Premenstrual tension with dysmenorrhoea for two years. No relief with analgesics. Chlorpromazine gives "considerable relief."

Results

The response to the drug has been considered from two points of view. In the first place we have noted the response of the patient as a whole unit to therapy, and these results are set out in Table I. "Much improved" includes cure or relief so substantial that no further treatment is required other than the continued administration of chlorpromazine at periodic brief interviews. "Somewhat improved" means relief of symptoms to a material degree appreciated by both patients and doctor, but leaving therapeutic work to be done. "No relief" includes slight relief.

TABLE I.—*Clinical Assessment of Results*

	Case Nos.	Total No. of Cases
Much improved ..	15, 21, 22, 23, 24, 25, 26, 27, 28, 29	10
Somewhat improved	4, 6, 8, 14, 17	5
No relief	1, 2, 3, 5, 7, 9, 10, 11, 12, 13, 16, 18, 19, 20	14

Our second approach to the results was to determine the effect of chlorpromazine upon *individual* features of each patient's symptom-complex so that we might determine whether any particular symptom responded irrespective of the diagnostic setting in which it occurred. These results are set out in Table II, and some duplication can be observed. Thus primary tension, secondary tension, and phobias could be distinguished in Case 5, which therefore appears in three columns.

TABLE II

Symptoms	Phobias	Depression	Obsessional Thinking	Psychogenic Pain	Non-psychogenic Pain	Diffuse Tension	Tension Following Obsessional Thinking
Much improved		21		3, 22, 27, 28		6, 15, 21, 22, 23, 24, 25, 26, 27, 28, 29	
Somewhat improved	6, 8, 16	17		29		3, 4, 5, 7, 8, 14, 17	5, 6, 8, 14, 15, 16, 17, 18
No relief	5, 7, 9, 17	11, 12, 13, 16	14, 15, 16, 17, 18	1, 2	19, 20	9, 1, 2, 10, 11, 12, 13, 16, 18	9

Discussion

We have tried to give adequate data to permit the drawing of some reasonably firm inferences, where homogeneity of results justifies this even in a small series. It is notable that *all* the cases in which tension was predominant were much improved. We should note, however, that no cases of *agitation* as opposed to tension occur in the series, and we have no observations to offer on the effect of chlorpromazine on such cases. Our three cases of dysmenorrhoea, which we regarded as basically tension states, were also "much improved." Of our 29 patients, 18 showed a significant degree of relief of tension.

Those patients with notable hysterical features, those with mainly phobic features, and the depressed did badly. Results in patients with predominant obsessional symptomatology were poor, except for one (Case 15) in whom the symptom was secondary to a depression.

With regard to pain, our series is too small for anything save the diffident suggestion that psychogenic pain appears to have been relieved, whereas in two cases which we have called "central" pain—probably due to arteriopathic changes in the brain—no relief occurred.

We have not, therefore, been able to confirm the findings of Sigwald and Bouttier concerning the relief given by chlorpromazine to patients with obsessional, depressive, or phobic symptoms. Nevertheless we are convinced of the value of the drug in alleviating tension both in its affective and in its muscular sense. In this respect our findings are similar to those of the French workers, but we cannot go further than that. We believe that all our good results, in whatever type of patient, are explicable on the grounds of relief of tension alone. This feature has been of great value in bringing some patients within the scope of psychotherapy who might otherwise have been outside it. A combination of chlorpromazine, psychotherapy, and relaxation treatment (Garmany, 1952) appears to give the best results at present obtainable in the treatment of the tension state.

Summary

A clinical investigation of the effects of chlorpromazine upon 29 psychoneurotics has not confirmed the value claimed for the drug in the treatment of "psychasthenic" illness.

Its value in the treatment of tension states appears to have been adequately established.

Toxic effects upon the liver have been noted in a few cases; and in two cases of hypertension an alarming tachycardia was observed despite treatment in bed.

We wish to thank Messrs. May and Baker, through whose courtesy supplies of "largactil" were made available.

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The number of permanent houses completed in Great Britain during June, 1954, was 30,973, compared with 26,598 in June, 1953. In the first six months of 1954, 167,695 permanent houses were completed, which was an increase of over 22,000 compared with the figures of the previous year. So far this year about 40,000 houses and flats have been built for sale. The number of houses and flats under construction on June 30, 1954, was 316,305, and the total number of permanent houses and flats completed in Great Britain since the war now amounts to 1,742,745.

TETANUS TREATED WITH TUBOCURARINE AND INTERMITTENT POSITIVE-PRESSURE RESPIRATION

BY

G. E. HONEY, B.M., M.R.C.P.
Senior Medical Registrar

B. E. DWYER, M.B., D.A., F.F.A. R.C.S.
Registrar in Anaesthetics

A. CRAMPTON SMITH, M.B., D.A., F.F.A. R.C.S.
Anaesthetist

AND

J. M. K. SPALDING, D.M., M.R.C.P.
Research Assistant, Department of Neurology

(From the Radcliffe Infirmary, Oxford)

The treatment of the severe case of tetanus which does not respond to sedation presents a difficult problem. The advent of relaxant drugs opened new possibilities, and reports appeared describing the use of curare, myanesin, and similar drugs in such cases (Cole, 1934; Plewes and Wilson, 1951; Schmidt *et al.*, 1953). The dose of relaxant which may be required to control severe tetanic spasms, however, may paralyse or severely weaken the respiratory muscles (Woolmer and Cates, 1952). Attempts have been made to treat such cases in tank respirators, but as paralysis of swallowing is also present it is very difficult even with the aid of a tracheostome to keep the airway clear. Treatment has remained unsatisfactory, and in the last 12 years 56 patients with tetanus have been admitted to the Radcliffe Infirmary, of whom 17 died, all except one with pulmonary complications (Bryce-Smith, 1954). Lassen (1953) and his colleagues during the epidemic of poliomyelitis in Denmark were the first to treat respiratory paralysis combined with inability to swallow by inserting a cuffed tube into the trachea through a tracheostoma, and providing ventilation through it by intermittent positive pressure. If this procedure is adopted in a case of tetanus, large doses of relaxant sufficient to prevent muscular spasms can be given. A case treated successfully in this way is described.

Case History

On May 29, 1954, a strong, heavily built road-mender, aged 42, was admitted to the Radcliffe Infirmary under the care of Dr. P. C. Mallam (R.I. 32137). Eight days previously he had knelt on a flint at the roadside, cutting the right knee; the wound was cleaned and two stitches inserted.

On May 28 he noticed a little discomfort in the jaw when eating his evening meal. The following morning his jaw and neck felt stiff. He consulted his doctor and was sent to hospital as a case of suspected tetanus. On admission the wound appeared clean and almost healed. *Clostridium tetani* were isolated from the tissue excised next day. He showed a characteristic risus sardonicus; there were slight trismus and a little stiffness of the neck. One hundred thousand units of anti-tetanic serum was given intravenously and sedation started with phenobarbitone and sodium amylobarbitone. Six hours later he had noticeable stiffness of the back and some difficulty in swallowing. Next morning the disease had progressed and early opisthotonos was present.

In view of this deterioration, it was decided to observe the effect of mephenesin ("myanesin") on the trismus and muscle stiffness, and on the vital capacity (see Table), before it became advisable to use a relaxant therapeutically. It was necessary to give mephenesin 2.0 g. intravenously to obtain satisfactory control of muscle spasm, but this also affected the pharyngeal muscles, leading to inhalation of fluids taken by mouth.

Time (Hours)	Intravenous Mephenesin (g.)	Maximum Separation of Gums (cm.)	Vital Capacity	Symptoms
0		2·1	1,330	Neck rigidity. Able to swallow
¼	1·0			
½		3·2	1,330	Unchanged
1		2·4	1,330	"
1¼	1·5			
1½		3·4	1,500	Neck rigidity diminished
2		3·1	1,400	Neck rigidity returned
2¼	2·0			
2½		3·6	1,630	Neck rigidity markedly reduced. Ptosis, dysarthria. Severe dysphagia
4		2·4	1,260	Condition as before injections

That evening, May 30, his condition had deteriorated further; he had a headache and was sweating, there was more stiffness of neck and back with occasional painful spasms of back muscles, and he complained of stiffness of the abdominal muscles. Difficulty in swallowing was more marked, so feeding by mouth was stopped and a polythene tube passed into the stomach. Two-hourly feeds of the type described by Higgins *et al.* (1954) were begun, about 3,500 calories being given per day. During the course of the next day he received mephenesin 1.0 g. through the nasal tube every two hours, and sedation was continued. In spite of this his condition steadily deteriorated, his temperature rose to 99.4° F. (37.4° C.), and he sweated profusely. That evening he had a slight generalized tetanic convulsion for the first time, and a further 100,000 units of anti-tetanic serum was given intravenously. By the next morning, June 1, he was having painful convulsions at intervals of one to eight minutes. It was decided to perform a tracheotomy, produce full muscular relaxation with curare, and maintain respiration by intermittent positive pressure through a short, cuffed, tracheal tube.

Muscular relaxation was maintained over the course of the next 24 hours, tubocurarine chloride, 15 mg., being injected intravenously whenever the patient showed signs of return of respiratory or other movement, usually every 40 minutes. Six hours later "tubadil," 100 mg. (a depot form of tubocurarine in a wax base), was given intramuscularly, and this prolonged to about two hours the intervals at which tubocurarine chloride had to be administered. Every two hours he was turned and all pressure areas treated. He was then tipped into the Trendelenburg position and percussion and vibration were applied to the chest to encourage drainage of secretions, which were then aspirated through the tracheostoma. Sedation was continued with sodium amylobarbitone, 0.2 g. every four hours by nasal tube, and he was given penicillin one million units and streptomycin, 0.5 g. intramuscularly, to prevent respiratory infection.

After 24 hours the injections of tubocurarine chloride were discontinued in order to assess progress, but the rest of the routine was continued. It was not until 24 hours later that muscular power recovered sufficiently for him to breathe unaided. He was then still aware of slight muscular spasms, but they were far less painful than they had been.

During the next 12 hours he was restless in spite of sedation. The generalized tetanic convulsions returned—at first only in response to stimuli such as turning and tracheal suction, but later spontaneously. The regime of full muscular relaxation and intermittent positive-pressure respiration was resumed and maintained for a further 72 hours. The requirements of tubocurarine chloride gradually

diminished so that injections were necessary only every two to three hours. Sedation with sodium amylobarbitone, 0.2 g. every four hours, was continued; this did not appear to be sufficient to induce sleep and was supplemented by thiopentone, 0.5 to 2.0 g. intravenously in divided doses at night. No further tubocurarine chloride was given after May 7, six days after this treatment was started. (Total dose: tubocurarine chloride 1,005 mg., tubadil 350 mg.)

Muscular power returned sufficiently to enable him to breathe unaided about 12 hours after the last dose of tubocurarine. The stiffness of the back and neck gradually returned, and there were occasional minor tetanic spasms in response to stimuli, especially tracheal suction. The whole clinical picture, however, was much less intense than it had been the week before. During the next four days there were intermittent attacks of bronchospasm, sometimes precipitated by suction down the tracheostoma, and sometimes by his own coughing. These were relieved by ephedrine, 16 mg. orally every four hours, and theophyllin with ethylene diamine 0.25 g. intravenously. The attacks of bronchospasm and the tetanic spasms were far less frequent when he was heavily sedated. During this stage of recovery he suffered from abdominal distension, which may have been an effect of the prolonged use of tubocurarine.

By June 12 he was swallowing well and the tracheal tube was removed. His progress was thenceforward relatively uneventful; the stiffness of the back and neck persisted for a further four weeks.

He was ambulant by the end of June, and discharged home, fully recovered, on July 16, having very little recollection of his illness from the time that he was anaesthetized for the tracheotomy until he had recovered and was taking food again.

Discussion

Large doses of relaxant were necessary to control the spasms, and artificial respiration by intermittent positive pressure made such doses possible. At the same time, the cuffed tracheal tube provided a barrier between the pharynx and the lungs. The procedure adopted was similar to that previously employed for cases of severe paralysis due to disease (Crampton Smith *et al.*, 1954). Intermittent positive pressure was provided by a mechanical pump (Russell and Schuster, 1953), and this uniform but controllable ventilation eliminated the laborious and inconstant process of squeezing an anaesthetic bag by hand. It should be emphasized that the details of treatment by this method are important, and, in particular, physiotherapy to the chest may be vital and should be vigorous. This is practicable, as the danger of provoking spasms has been removed.

Two special problems arise in treating tetanus in this way: the use of the relaxant, and the choice of the sedative.

Relaxant

Tubocurarine proved satisfactory in this case. The need for a relaxant in cases of this type continues for several days at least, and possibly for two and a half weeks (Bjørneboe, Ibsen, and Johnsen, 1953), during which time many intravenous injections are required. It is convenient to give these into a continuous intravenous infusion, but between injections the minimum of fluid should be given by this route. Succinylcholine ("scoline") was the relaxant used by Shackleton (1954), but to use a relaxant with so short an action for an illness of such length is not ideal. Rapid return of muscle tone is undesirable, and since respiration is artificial overdosage carries no risks. Tubocurarine has, moreover, been preferred to succinylcholine on the grounds that the latter tends to produce increased bronchial secretions (Ibsen, 1953). A long-acting relaxant is desirable, at least to give a basal level of relaxation, and the intramuscular "depot" preparation of tubocurarine which this patient received appeared to reduce the frequency at which intravenous injections were required. It is likely that when a depot form of curare becomes generally available it may be the drug of choice for this purpose.

As muscle tone returns it becomes increasingly difficult to inflate the lungs; warning of this is given by a rise in the inspiratory pressure indicated by a pressure gauge placed at the mouth of the tracheal tube. The ventilatory minute volume is decreased, and there may be a rise in the blood pressure due to carbon dioxide retention. Unlike pulmonary atelectasis, which also causes an increased resistance to inflation, these effects can be reversed by a further dose of relaxant.

Sedative

Patients have been almost completely paralysed by disease and treated by artificial respiration with intermittent positive pressure. On recovery they have had no regrets that they were conscious during their illness. It is possible, therefore, that a patient paralysed by a relaxant will only require a minor degree of sedation provided he is relieved of the pain due to muscular spasm. Volunteers have found it unpleasant to be paralysed by a relaxant and yet conscious. It is perhaps humane to keep any patient treated by the method here described in an unconscious or semi-conscious state. Ibsen and his colleagues (Bjørneboe, Ibsen, and Johnsen, 1953) and Shackleton (1954) anaesthetized their patients with continuous nitrous oxide and oxygen in a semi-closed circuit, using soda-lime as a carbon-dioxide absorber. The advantage of nitrous oxide is its low toxicity and rapid elimination. Its use introduces the extra hazards that a cylinder may run out unnoticed, or be replaced by another of the wrong gas. The latter disaster occurs even in the operating theatre, and in a case such as this, where many of the staff will not be experienced in anaesthetic work, the danger will be proportionately greater. Gases in cylinders are expensive, and it is difficult to maintain their supply when used continuously. Other inconveniences may be introduced by the necessity of using soda-lime.

Barbiturates have much in their favour as sedatives. A medium-acting one, such as sodium amylobarbitone, can be given regularly to maintain a constant level of sedation, and this can be supplemented by intravenous thiopentone. Large amounts of barbiturates may be required, and the immediate danger of barbiturate poisoning—namely, respiratory arrest—is eliminated, since respiration is controlled. No late ill effects of massive doses of barbiturates were observed in this case.

Summary

A patient with severe tetanus failed to respond to sedation and mephenesin. He was treated with paralysing doses of tubocurarine, and artificial respiration was maintained mechanically by intermittent positive pressure through a cuffed tracheal tube. Recovery was complete. The use of relaxants and the choice of sedative in this form of treatment are discussed.

We are grateful to Dr. P. C. Mallam, under whose care this patient was treated, for permission to publish, and to Professor R. R. Macintosh for his helpful advice. We are indebted to Mr. R. G. Macbeth, who performed the tracheotomy; and to Dr. Ritchie Russell for his assistance, and for introducing mechanically operated, intermittent positive-pressure respiration to this hospital. We must also thank the nurses and all those doctors who contributed so much to the patient's recovery. Dr. Bryce-Smith kindly provided supplies of tubadil, which was manufactured by Endo Products Inc., New Jersey.

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FATAL TETANUS IN A BOY AFTER PROPHYLACTIC TETANUS ANTITOXIN

BY

A. H. M. LITTLEWOOD, F.R.C.S.
(From the Epsom District Hospital)

A. K. MANT, M.D.

AND

G. PAYLING WRIGHT, D.M., F.R.C.P.
(From Guy's Hospital Medical School)

The use of antitoxic serum as a specific prophylactic for the prevention of tetanus after injury is now so general that any occasion of failure merits careful consideration. A case of tetanus is here recorded in which, in spite of the accepted prophylactic dose of antitoxin within two hours of the accident, the patient contracted and died from tetanus. In this instance, as is discussed below, the failure appears to be attributable to a state of hypersensitivity to the foreign serum proteins that had been induced by a similar prophylactic injection given six months before.

Case Report

A schoolboy aged 14 was admitted to hospital on June 25, 1953, having injured his left hand when experimenting with an explosive mixture of sulphur, phosphorus, and potassium chlorate. An explosion of this mixture caused lacerations of the fingers, with some full-thickness skin loss. He was given 1,500 international units of antitetanus serum on admission and his injuries were treated by cleansing, debridement, suture, and the application of free skin grafts. He received a ten-days course of penicillin, 200,000 units six-hourly (8 million units in all).

On December 29, just six months later, he was readmitted with lacerations of the left hand, abdomen, and thigh due to the explosion of a similar mixture packed into a metal tube. He was given a prophylactic dose of 1,500 I.U. of A.T.S. after he had failed to produce any reaction to a subcutaneous test dose of 0.1 ml. He was treated as before by cleaning, debridement, and suture of the lacerations with the application of split-thickness skin grafts to areas of full-thickness loss on the fingers. He again received a course of penicillin, 500,000 units of soluble penicillin initially followed by 300,000 units of procaine penicillin daily (6,200,000 units in all).

On January 10, 1954, twelve days after the injury, a diagnosis of tetanus was made when the patient complained of difficulty in swallowing and showed trismus and stiffness of the erector spinae muscles.

Arrangements were made to give a treatment dose of A.T.S., and, in view of the recent previous administration of horse serum, a test dose was given which produced a mild urticarial reaction. Accordingly, he was desensitized by the administration of 0.025 ml. subcutaneously, the dose being doubled every 15 minutes until 1 ml. had been given. Then 1 ml. was given intravenously, and on the injection of the first 0.1 ml. a considerable reaction was produced; the skin of the face and neck became bright red, and the pulse rate rose from 80 to 180 a minute and the respirations from 20 to 40 a minute. When the reaction had subsided, the rest of the injection and a further 86,000 units of A.T.S. were given intravenously without further reaction (100,000 units in all). The septic wound on the hand and the wound of the abdomen were then excised to prevent the further absorption of toxin.

Tetanic spasms began on the following day and were at first of a few minutes' duration, but later lasted from ten to twenty minutes. They occurred about once or twice an hour and increased in severity. Their effects were mitigated by the subcutaneous administration of a saline drip containing hyalase and succinylcholine chloride ("scoline"), 1:1,000.

On January 12 tracheotomy was performed, the more easily to aspirate the bronchial secretions and swallowed sputum which embarrassed respiration. The patient showed no signs of improvement and died on January 15, five days after the first appearance of symptoms and seventeen days after receiving his injury.

Necropsy Report

A necropsy was carried out seven hours after death. The deceased was well nourished and of normal development for his age. The following injuries were present: (1) Extensive lacerations of the skin of the left palm and of the palmar surfaces of the left thumb and first and middle fingers. These lacerations had been recently reopened and the deep tissues widely exposed. There was no gross sepsis present. The pattern of these fresh injuries was similar to that of the injuries received on June 25, 1953, but from the remnants of the old skin-grafts remaining they appeared to be slightly less extensive. (2) A wound had been excised in the right iliac fossa, and an oval area of skin and subcutaneous tissue 6–7 cm. across had been removed. (3) A superficial wound, 1–2 cm. in diameter, over the left anterior-superior iliac spine involving cuticle only. (4) A wound which externally appeared identical with No. 3 above was present on the anterior surface of the left upper thigh. Dissection, however, revealed that this was in fact a penetrating wound, and some cloth fibres were found in its depth lying on the deep fascia.

Internal examination revealed an acute suppurative bronchopneumonia of the hypostatic type, some acute fatty degeneration of the myocardium and liver, and granulocytosis of the spleen. The rectus abdominis muscles were intact.

Tissues were excised from the wounds, and these together with the cloth fibres were examined for *Cl. tetani* without success.

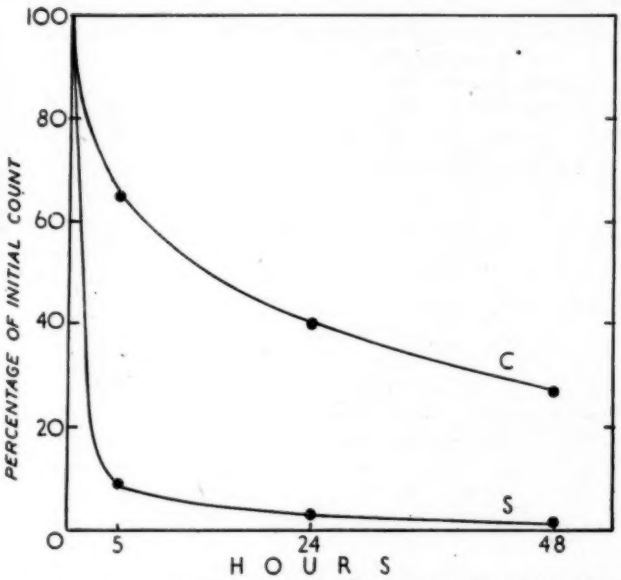
Discussion

The general question of the influence of hypersensitivity to horse serum on the duration of passive antitoxic immunity in man has been reviewed by Robertson (1916) and by Schmidt (1934). Among a number of equivocal records, two studies are notable for their careful execution and informative results. The first was made by Park and Zingher (1916), who found by comparative Schick tests that the period of passive immunity that followed a second inoculation with diphtheria antitoxin lasted only about half as long as that which followed the first. In the second, Hooker and Follensby (1931) determined the duration of the passive immunity to the Dick erythrogenic toxin that followed an intradermal inoculation of the specific antitoxin in the following three groups of persons: normal controls and "immediate reactors" and "delayed reactors" to tests with horse serum. They found that the controls and the "delayed reactors" usually retained an effective portion of the test dose of antitoxin at the local site for more than 24 hours, whereas in the "immediate reactors" the antitoxin lost its potency in less than four hours.

In experiments upon specifically sensitized animals, Glenny and Hopkins (1923–4) clearly demonstrated that foreign proteins such as those of serum are removed from the circulating blood much more rapidly than from the blood of control animals, and their findings have since received support from studies made with antigens labelled with radioactive isotopes. Talmage *et al.* (1951) observed that rabbits which had had previous parenteral exposure to bovine gamma-globulin, but in whose blood no specific circulating antibody could be detected at the time of the second injection, eliminated the gamma-globulin at a rate similar to that of the control

animals for two days and *then at a sharply accelerated rate*. On the other hand, rabbits with some demonstrable specific circulating antibody at the time of reinjection showed a precipitate fall in the concentration of the antigen in the blood *which began at the moment* of the injection. Laws and Payling Wright (1952) also observed a striking difference in the rates of disappearance of bovine serum albumin from the circulating blood of control and specifically immunized rabbits (see Chart), and found that within a few minutes of its injection into the latter animals much of the antigen had been removed by the liver.

From studies on both human beings and animals there thus seems to be concordant evidence that previous experience of a soluble antigen—and among these diphtheria and tetanus horse-serum antitoxin must be included—leads to a much accelerated removal from the circulating blood



Radioactivity of blood of control (C) and sensitized (S) rabbits at various intervals after the intravenous injections of radio-iodinated bovine serum albumin (from Laws and Payling Wright, 1952).

on a second or subsequent injection, and consequently to a curtailment of any effectiveness that it may possess as a passive prophylactic agent.

One important practical conclusion emerges from the present discussion. Once a person has received an injection of any horse-serum antitoxin, irrespective of the disease for which it may have been given, that person should be promptly immunized against diphtheria and tetanus with the appropriate toxoid. By thus creating the state of active immunity, which can be effected without any unpleasant side-effects, any future need for passive protection against these diseases with horse-serum antitoxin is rendered unnecessary. Furthermore, before any surgical measures are undertaken in tissues which have been previously traumatized and may in consequence harbour contaminating tetanus spores, active immunization should always be undertaken shortly beforehand as a precautionary measure.

We wish to express our thanks to Mr. E. N. Callum for his permission to publish this case report and to Dr. J. Murray Robertson, H.M. Coroner for West Surrey, for permission to publish the necropsy findings.

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MEPHENESIN AND GALLAMINE TRIETHIODIDE IN TETANUS

BY

C. MURRAY PARKES, M.B., B.S.

Lately Senior House-physician, Kettering and District General Hospital

The majority of deaths from tetanus result either from tetanic spasm and exhaustion or from pulmonary complications. In many cases the symptoms will be so mild that simple sedation with barbiturates or paraldehyde is all that is required, but these cases will get better whatever the treatment and are not discussed here. In severe cases, however, it is imperative to prevent, or at least relieve, the tetanic spasms, and to this end we have used a continuous intravenous infusion of normal saline into which the appropriate drug can be injected.

The choice of relaxant depends upon the severity of the case and development of tolerance to the relaxant. Thus, Smith and Thorne (1952) showed that steadily increasing doses of gallamine triethiodide were required, and we have noted a similar tolerance to mephenesin. Curare has been found unsatisfactory in tetanus because of the narrow borderline between relaxing and paralysing doses. (In seven cases reported by Godman and Adriani (1949) treatment was regarded as unsatisfactory for this reason in all cases.) Like curare, gallamine triethiodide is thought to act by blocking transmission across the myoneural junction of voluntary muscle, but the margin of safety between relaxation and respiratory paralysis is greater and the occurrence of histamine-like reactions to gallamine is rare. The mode of action of mephenesin is not fully understood, but is believed to be the result of selectively depressing reflex hyperexcitability in the spinal cord without greatly affecting neuromuscular transmission. Thus respiratory depression is minimal. On the other hand, mephenesin produces haemolysis (Wilson and Gordon, 1948), and this may prevent sufficient being given to control the spasms.

Case Report

A well-built man aged 22 had for some weeks been engaged in operating an excavator in the digging of a 50-ft. (15-metre) sump in cultivated land. On the evening of March 17, 1953, he noticed that his jaw was a little stiff. This became progressively worse, and when admitted to the Kettering General Hospital on March 19 he had only ¼ in. (6 mm.) separation of the jaws; there was increased tone in all voluntary muscles, and board-like rigidity of the abdomen. A thorough examination revealed no signs of skin abrasion or injury.

He was given 100,000 units of tetanus antitoxin intravenously (this was repeated one week later), soluble penicillin, 500,000 units four-hourly, and 4 dr. (14 ml.) of paraldehyde in 100 ml. of saline rectally. In spite of this, within a few hours of admission painful muscle spasms began, increasing in frequency and severity during the next four days. On March 20 an intravenous infusion of normal saline was set up and run in at the rate of 1 pint (570 ml.) in eight hours, 5,000 units of heparin being added to each pint of saline. In this way the drip was kept going for nine days with only one change of vein. In order to control the spasms a 10% solution of mephenesin ("myanesin") was injected into the drip tubing in doses of 5–10 ml. This was followed by immediate relief of the spasm accompanied by a feeling of tiredness and transient "drunkenness." In an attempt to reduce the general muscular rigidity between spasms the patient was also given mephenesin by

mouth (" elixir of myanesin ") 1 fl. oz. (1 g.) five times daily, and 30 ml. of the 10% solution was added to each bottle of normal saline.

The dosage of mephenesin needed to control spasms rose day by day, and it is hardly surprising that, five days after starting mephenesin, haemoglobinuria occurred. This followed the administration of 21.5 g. of mephenesin in the preceding 24 hours (331 mg. per kg.). Within 24 hours of stopping mephenesin the urine was clear and there was no haemoglobin to spectroscopic examination. The blood urea was 36 mg. per 100 ml.—and the patient experienced no ill effects from the incident.

In place of mephenesin, gallamine triethiodide (" flaxedil ") was now given into the drip tubing and was followed by immediate loss of spasm and pain with rather more tiredness and drunkenness than had occurred with mephenesin. The maximum single intravenous dose was found to be ½ ml. (10 mg.), for on the occasion when 0.75 ml. was given complete paralysis of voluntary and respiratory muscles took place and the patient became deeply cyanosed. Oxygen was administered under pressure and artificial respiration maintained for a short time until normal respiration was re-established.

Coincident with the beginning of gallamine therapy the patient's temperature rose and he developed signs of patchy collapse at the right base. He was a little troubled at this time by the accumulation of secretions in his chest, which he was unable to cough up because coughing provoked generalized spasms. On March 27 striking improvement became apparent. Spasms diminished in intensity and frequency, and the amount of gallamine required to control them fell correspondingly. As the spasm diminished so the patient's respiratory condition improved, and he made an uneventful recovery.

Comment

The absence of respiratory depression with mephenesin makes this a highly useful drug in the treatment of tetanus. Intravenous administration gives maximal relief of spasm and is less disturbing to the patient than frequent intramuscular injections. It has the disadvantage that increasing dosage is required, and it is probably dangerous to press mephenesin therapy to the point of haemoglobinuria; indeed, Hewer and Woolmer (1947) report a death following its administration.

Gallamine triethiodide should be reserved for those cases which fail or cease to respond to mephenesin, since gallamine carries a very real risk of respiratory depression, and the borderline between relaxation and complete paralysis of all voluntary muscle is small. Again, intravenous administration is advisable, since intramuscularly its effect is difficult to control and it is a painful injection.

I wish to thank Dr. Thomas Partington, consultant physician, Kettering and District General Hospital, for his advice and criticism during the preparation of this article.

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The Central Youth Employment Executive has recently published three more booklets in the " Choice of Careers " series. These deal with the medical laboratory technician, the occupational therapist, and the physiotherapist respectively, and give an account of the technical qualifications, professional training, day-to-day work, and salaries and prospects in these three medical auxiliary services. The " Choice of Careers " booklets are intended primarily for young people who are deciding the type of work to take up, and also for those who are concerned in helping them to make a suitable choice of career. The booklets are obtainable from Her Majesty's Stationery Office, price 6d. each.

THE FLUORESCEIN CIRCULATION TIME IN THYROTOXICOSIS

BY

A. GEE, M.R.C.P.

Late Medical Registrar, Watford Peace Memorial Hospital

A hyperkinetic circulation is an almost axiomatic feature of thyrotoxicosis. Blumgart *et al.* (1931) first demonstrated an increased speed of pulmonary blood flow in this condition. Wood (1950) stated that cardiac outputs of up to 12 litres a minute occur in thyrotoxicosis, and that increased outputs often do not subside for several weeks after the basal metabolic rate returns to normal. Goldberg (1938), in a study of 72 thyrotoxic subjects, demonstrated definite shortening of the circulation time in every instance. Unfortunately, the calcium gluconate method employed does not give an accurate end-point, and a control series of cases was not included. Moreover, other causes of circulatory acceleration were not considered.

In the measurement of circulation times the chief requisite is a method giving an objective and instantaneous " end-point." The fluorescein method described by Macgregor and Wayne (1951) fulfils these needs, and is safely and easily performed.

In this investigation the circulation times of 26 thyrotoxic subjects are compared with 14 euthyroid cases of thyroid enlargement and 20 cases of acute anxiety state. At the outset it was found that occasional cases of anxiety state had shortened circulation times when not sedated. Therefore, every case included in this investigation was given soluble amylobarbitone, 6 gr. (0.4 g.), one hour before the test was performed.

Technique

The technique used was a minor modification of Macgregor and Wayne's method. The test is briefly explained to the patient beforehand. This allays anxiety, and often evokes willing and interested co-operation. The requisites are : (1) A darkened, warm room. The ray-therapy room of a physiotherapy department was found to be ideal after fitting a blind to the window. (2) An ultra-violet lamp, fitted with Wood's diagnostic filter. This concentrated the radiation at a wave-length evoking the maximal fluorescence of fluorescein. (3) Ampoules of 4 ml. of sterile 20% fluorescein solution. (4) An equal mixture of histamine 0.1% (1:1,000) and procaine 2% solutions.

The patient, well clothed and wearing woollen socks, is warmed with an electric blanket until sweating is induced, and, wrapped in several blankets, is then rapidly transported to the darkened room.

Using the histamine-procaine mixture, intradermal weals are made at the left antecubital fossa and at the lateral aspect of the base of each hallux. The patient is kept warm whilst the weals develop; when possible, it is a good plan to keep the feet exposed but heated by a radiant-heat lamp. The fluorescein ampoule is now opened and the contents are prepared for intravenous injection. An assistant stands by the electric-light switch with a stopwatch. He switches off and starts timing at the command " go," and records two times at the commands " now " and " stop." The commands are given by the operator at the beginning of rapid intravenous injection at the right antecubital fossa; at the first appearance of fluorescence at the left antecubital fossa; and at the first appearance of fluorescence at the feet.

The end-points are clear and instantaneous, being given by sudden bright fluorescence of the weals. In timing, fractions of a second were not recorded, but were counted to the following second.

The difference between the arm-to-arm and arm-to-feet times is the "foot-minus-arm" time and, eliminating the variables of pulmonary circulation, is normally constant between 8 and 13 seconds.

Side-reactions.—These are trivial, and consist of: (1) Momentary flushing. Nausea may occur immediately following the injection, and is rarely accompanied by vomiting. It is preferable not to perform the test less than one hour after food. (2) Local reactions; 20% fluorescein has a necrotizing effect if injected extravenously. Thus the intravenous site of the needle should always be confirmed before extinguishing the lighting.

TABLE I.—*Thyrotoxic Patients*

Case	Sex	Age	Clinical Features	B.M.R.	Ancillary Investigations	Circn. Time Foot-minus-arm
1	F	50	Bilateral exophthalmos, weight loss	+56%	A.S.P. 82. S. chol. 90. S. creat. 0·9	4 secs.
2	F	51	Goitre, weight loss, tachycardia	+17%	A.S.P. 85. S. creat. 1·06	6 ,,
3	F	28	Goitre, hyperhidrosis, lassitude, weight loss	+36%	A.S.P. 94. S. chol. 98	3 ,,
4	M	26	Goitre, early exophthalmos	+56%	S. chol. 118. S. creat. 1·06. Histology positive	7 ,,
5	F	41	Exophthalmos (severe), minimal thyroid enlargement	+32%	A.S.P. 80	5 ,,
6	F	53	Goitre with vascular bruit, tachycardia, exophthalmos	+41%	A.S.P. 86. Histology positive	7 ,,
7	F	28	Goitre with vascular bruit, tachycardia, exophthalmos	+98%	A.S.P. 92. S. chol. 127. S. creat. 0·92	2 ,,
8	F	45	Goitre with vascular bruit, active rheumatoid arthritis	+21%	A.S.P. 86. S. chol. 92	6 ,,
9	F	31	Goitre with vascular bruit, tremor, sweating	+33%	A.S.P. 85. S. creat. 1·4. Histology positive	6 ,,
10	F	56	Nodular and retrosternal goitre, auricular fibrillation and congestive cardiac failure	+54%	S. chol. normal. Histology negative	6 ,,
11	F	24	Partial thyroidectomy 1946, loss of weight, tachycardia, recurrent goitre with vascular bruit	+91%	A.S.P. 80. S. chol. 125	2 ,,
12	F	62	Goitre, auricular fibrillation and congestive cardiac failure	+57%	Radioactive iodine uptake increased. Histology carcinoma	4 ,,
13	M	46	Goitre, exophthalmos, tachycardia	+43%	A.S.P. 80. Histology positive	5 ,,
14	F	32	Thyroid enlargement with vascular bruit, cachexia	+38% +35%	Radioactive iodine uptake increased	4 ,,
15	M	34	Goitre with vascular bruit, tachycardia	+51%	A.S.P. 84. Histology positive	6 ,,
16	F	24	Goitre, proptosis, hysteria	+22%	S. creat. 0·96	7 ,,
17	F	58	Goitre, lid-retraction, hysteria	+52%	A.S.P. 86. S. creat. 1·12	5 ,,
18	F	22	Exophthalmos, weight loss	+32%	S. chol. 72. Histology positive	4 ,,
19	F	41	Goitre with vascular bruit	+49%	A.S.P. 88. S. creat. 2·1. Histology positive	4 ,,
20	F	63	Thyroid "adenoma," exophthalmos and lid-retraction	+25%	A.S.P. 85. S. chol. 120	7 ,,
21	F	23	Goitre, exophthalmos, cachexia	+74%	A.S.P. 102. S. chol. 68	3 ,,
22	F	37	Goitre, dyspnoea, tachycardia, psychosis	+41%	S. chol. 122. Histology positive	13 ,,
23	F	39	Exophthalmos, auricular fibrillation	+62%	S. chol. 97. Histology positive	3 ,,
24	M	38	Goitre, obesity, tachycardia, lid-retraction	+40%	A.S.P. 86	7 ,,
25	M	40	Goitre with vascular bruit, exophthalmos, lid-retraction	+68%	A.S.P. 90. S. chol. 100. Histology positive	5 ,,
26	F	29	Goitre with vascular bruit, lid-retraction	+89%	A.S.P. 96. S. creat. 1·2	3 ,,

A.S.P.=Average sleeping pulse rate per minute. S. chol.=Serum cholesterol in mg. per 100 ml. S. creat.=Serum creatine in mg. per 100 ml.

A yellow appearance of the skin may be disturbing, but the subject should be reassured and told that the fluorescein will be rapidly excreted in the urine.

Thyrotoxic Cases

Table I shows some details of 26 thyrotoxic patients; in every case thyroid enlargement was present. Thyrotoxicosis was diagnosed clinically, before detailed investigation, in 23 cases. Apart from classical physical signs of thyrotoxicity, considerable diagnostic value was attached to the presence of a to-and-fro vascular bruit on auscultation over the thyroid gland. This sign was present in 10 of the thyrotoxic cases, but was not found in any of the 14 euthyroid cases of thyroid enlargement listed in Table II.

The following routine investigations were performed in the assessment of thyroid function: (1) Basal metabolic rate (B.M.R.). This is shown as a plus or minus figure, representing percentage deviation from average normal. (2) "Average sleeping pulse rate" (A.S.P.). This is the average of five nightly estimations, each taken from the temporal pulse during deep sleep, without waking the patient. Boas (1932) first drew attention to the value of this simple often-neglected investigation—which is of considerable use if common-sense precautions are taken in its execution. An A.S.P. of 80 a minute or more was regarded as supporting a diagnosis of thyrotoxicosis. (3) Serum cholesterol values of under 120 mg. per 100 ml. were regarded as supporting a diagnosis of thyrotoxicosis. (4) Serum creatine was estimated by the method of Peters (1942), and values of over 0.5 mg. per 100 ml. were regarded as supporting a diagnosis of thyrotoxicosis. (5) Thyroid histology, when available post-operatively or at post-mortem examination, was studied by the same pathologist on each occasion. Appearances suggestive of thyrotoxicosis are shown in Tables I and II as "histology positive"; in all cases in which the histological appearances were indefinite this is shown as "histology negative." (6) The radioactive iodine uptake was estimated in only two cases. With the exception of the B.M.R., which is tabulated separately, all investigations

TABLE II.—*First Control Series. Euthyroid Patients*

Case	Sex	Age	Clinical Features	B.M.R.	Ancillary Investigations	Circn. Time Foot-minus-arm
1	F	38	Partial thyroidectomy for "toxicity," 1943. Weight loss, nervous symptoms, and migraine. No thyroid enlargement	+24	Negative	10 secs.
2	F	26	Thyroid enlargement. Tachycardia and nervous symptoms	−1	,,	12 ,,
3	F	19	Goitre and nervous symptoms	+15	Negative, save S. creat. 0·64	12 ,,
4	F	32	Goitre; loss of weight, lassitude	−9	Negative	15 ,,
5	F	18	Goitre; dyspnoea	−3	,,	9 ,,
6	F	32	Partial thyroidectomy for "toxicity," 1943. Persistent exophthalmos	+22	,,	1· ,,
7	F	47	Goitre. Dyspnoea with stridor	+14	Negative. Histology negative	10 ,,
8	F	69	Dyspnoea. Retrosternal goitre on radiography	+6	,, ,,	17 ,,
9	M	25	Goitre with recent increase size	−9	Negative	9 ,,
10	F	53	Goitre; paroxysmal dyspnoea, severe hypertension	+12	,,	13 ,,
11	M	32	Dyspnoea, lassitude, tachycardia, tremor	+11	,,	14 ,,
12	F	33	Paroxysmal tachycardia. Minimal thyroid enlargement	−2	,,	8 ,,
13	F	57	Loss of weight, tremor, dyspnoea	+15	,,	15 ,,
14	F	30	Goitre, loss of weight, and tracheal compression	−6	Negative. Histology negative	9 ,,

are included in the section headed "ancillary investigations." Only results relevant to a diagnosis of thyrotoxicosis are shown in this column.

Of the 26 cases, 25 showed a shortened circulation time, the curious exception (Case 22) having a psychosis (agitated depression) necessitating certification some two weeks post-operatively.

In eight cases the circulation time was re-estimated after apparent restoration to euthyroidism following medical or surgical treatment. In two cases a hyperdynamic circulation persisted—one six months after partial thyroidectomy and another after 22 months' thiouracil treatment.

First Control Series

Table II shows details of 14 cases with thyroid enlargement and associated symptoms, or with persistent symptoms following partial thyroidectomy for thyrotoxicosis. All were clinically adjudged euthyroid. In Cases 7, 8, and 14, thyroidectomy was subsequently performed—one for retrosternal extension and two for tracheal compression. In one case (No. 1) cautious medical treatment was undertaken, in deference to a raised B.M.R. reading, associated with a past history of partial thyroidectomy. It is noteworthy that no case in this group had vascular bruit over the thyroid gland. All members of this group had normal circulation times.

Second Control Series

Table III shows some details of 20 patients in whom a psychiatric diagnosis was eventually established. None had thyroid enlargement, and in no instance was a diagnosis of thyrotoxicosis made on clinical grounds. All were followed up for short periods of up to three months. Most of these were cases of acute anxiety state in whom dyspnoea, tachycardia, or loss of weight featured prominently. For obvious reasons it was not desirable to admit all cases to hospital for detailed investigation.

TABLE III.—*Second Control Series*

Case	Sex	Age	Clinical Features	Circulation Time (Foot-arm)	Remarks
1	F	54	Agitated depression	20 secs.	Marked improvement on E.C.T.
2	M	40	Cardiac neurosis	8 „	B.M.R. +6. Improved on sedation and re-assurance
3	M	25	Hysterical hyperpnoea. Early schizophrenia	6 „	Transferred to psychiatric hospital
4	F	47	Menopause. Cardiac neurosis	11 „	B.M.R. −2. Improved on sedation and re-assurance
5	F	18	Hysterical hyperpnoea	10 „	Recovery on sedation and psychotherapy
6	M	28	Acute anxiety. Attacks of tachycardia and sweating	9 „	B.M.R. +5. Improved after sedation, cardiac investigation, and re-assurance

Cases 7 to 20 were out-patients with acute anxiety state. All of these showed "foot-minus-arm" circulation times within a range of 9 to 17 seconds.

The circulation time was within, or above, the normal range in 19 instances, the only case with a hyperdynamic circulation (No. 3) having a psychosis.

Discussion

Several causes of hyperkinetic circulation are now recognized, and it is therefore necessary to exclude them before a shortening of circulation time can fairly be attributed to thyrotoxicosis. These causes include pregnancy, anaemia, aortic incompetence, Paget's disease of bone, advanced hepatic failure, arteriovenous aneurysm, beriberi. These conditions are easily separated from thyrotoxicosis, and their exclusion rarely creates a problem, with the possible exception of vitamin-B deficiency.

Williams *et al.* (1943) found biochemical evidence of thiamine deficiency in 75% of a group of 40 unselected thyrotoxic subjects, and regarded this as being due to a combination of increased requirement and excretion of thiamine.

Since Wenckebach (1934) and other investigators have demonstrated a hyperkinetic circulation in beriberi, it is possible that vitamin-B deficiency of subclinical degree may be a factor in the circulatory acceleration of thyrotoxic subjects. This may explain some discrepancies in either degree or duration of hyperkinesis, but does not affect the first finding of this investigation—that virtually all thyrotoxic subjects have some degree of circulatory acceleration.

The second finding is that psychogenic disturbances, under amylobarbitone sedation, do not result in hyperkinesis. Thus a relatively simple test can be used to resolve the differential diagnosis of thyrotoxicosis and uncomplicated anxiety state.

Summary

The circulation time, calculated by the method described, is considered to be a valuable ancillary investigation in the diagnosis of thyrotoxicosis, provided other causes of hyperdynamic circulation are recognized and excluded.

The method used is regarded as safe and easy; in several instances it was performed on out-patients.

In a group of 26 thyrotoxic cases, 25 had a circulation time below normal limits.

In a group of 20 psychiatric cases, only one case had a shortened circulation time.

In a group of 14 euthyroid patients with thyroid enlargement, all cases had normal circulation times.

My thanks are due to Dr. J. S. Richardson for his invaluable help and criticism, to Dr. C. Pyke for histological reports, and to the physicians who kindly supplied the bulk of my clinical material.

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TREATMENT WITH INSULIN ZINC SUSPENSIONS

BY

G. MELTON, M.D., M.R.C.P.
Consultant Physician, Highlands General Hospital, London

Further evidence regarding the results of insulin zinc suspension therapy is provided by the series of 52 patients reported here. Treatment was given in the wards in 36 of these cases, the remainder being treated throughout as out-patients. This trial has been in progress for the past nine months.

Results were classified as good if the fasting, noon, and evening blood sugars (estimated by King's method) were within normal limits, such results being confirmed by further satisfactory urine and blood-sugar tests.

The quantity of carbohydrate in the diets varied from 140 to 250 g. a day, generally divided into approximately equal rations at the four main meals, with snacks at mid-morning and bedtime. In some cases in which the noon blood sugars remained high as compared with those later in the day, the carbohydrate was reduced at breakfast, more being given at lunch and/or the later meals.

Results

The results are summarized in Table I. In the whole series good control with insulin zinc suspension (I.Z.S.) alone was obtained in 42 patients, 16 of whom had had no previous insulin treatment. Four other patients were reasonably well controlled with I.Z.S. mixtures, two requiring the further addition of the "amorphous" preparation and two the addition of the "crystalline" preparation to the I.Z.S. The doses required for stabilization exceeded 50 units in nine patients. Seven of the successfully treated patients showed improved control over that obtained with previous insulin therapy.

TABLE I.—*Summary of Results of Treatment of 52 Patients with Insulin Zinc Suspensions*

Previous Insulin Therapy	No. of Cases	Type of Insulin Zinc Suspension	Results of Treatment	
			Good	Poor
None ..	16	I.Z.S.	16	—
S.I. b.d.	9	I.Z.S.	7	2
	3	I.Z.S.+I.Z.S.A.	2	1
S.I.+P.Z.I.	18	I.Z.S.	15	3
	2	I.Z.S.+I.Z.S.C.	2	—
P.Z.I. ..	1	I.Z.S.	1	—
G.I.	3	I.Z.S.	3	—

S.I.: Soluble insulin. P.Z.I.: Protamine-zinc insulin. G.I.: Globin insulin. I.Z.S.: Insulin zinc suspension. I.Z.S.A.: Insulin zinc suspension (amorphous). I.Z.S.C.: Insulin zinc suspension (crystalline).

The six cases not successfully controlled by I.Z.S. (Table II) had previously been on older insulin therapy, although two of them had not been well controlled just before starting I.Z.S. There was rapid worsening of the diabetic state in some of these patients, particularly in Cases 1, 2, and 3, which had been well controlled on two daily injections of soluble insulin. Because of this and the time which would have been needed for further experimenting with I.Z.S. mixtures, it was found necessary to return these patients to their older insulin therapy.

TABLE II.—*Data of 6 Cases Showing Poor Response to Insulin Zinc Suspensions Following Transfer from Older Insulins*

Case No.	Previous Insulin (Units)	Blood Sugars			Insulin Zinc Suspension (Units)	Blood Sugars		
		F	N	E		F	N	E
1	S.I. b.d. 24+12	156	82	177	I.Z.S. 60	446	364	275
2	S.I. b.d. 38+26	184	106	158	I.Z.S. 72	235	336	206
3	S.I. b.d. 28+12	122	85	107	I.Z.S. 44	332	495	535
					I.Z.S.A. 24+ I.Z.S.C. 30	140	136	296
4	S.I. 24+P.Z.I. 20	172	120	96	I.Z.S. 56	342	394	136
5	S.I. 30+P.Z.I. 24	256	147	215	I.Z.S. 76	294	403	203
6	S.I. 14+P.Z.I. 18	400	272	206	I.Z.S. 40	240	360	496

F=Fasting. N=Noon. E=Evening.

Hypoglycaemic Reactions.—These were marked in only two patients, despite the occasional finding of low blood sugars in others.

Local Reactions.—Only one patient showed local inflammatory reactions at the sites of injection for several weeks. One other patient developed insulin atrophy of the abdominal wall, which he had been using exclusively for his injections.

Discussion

In view of the high proportion of successes with I.Z.S. recorded here and by other observers, it is justifiable to try this preparation in all new cases requiring insulin therapy, unless the presence of a severe infection or marked ketosis makes initial treatment with soluble insulin advisable. The marked infrequency of local reactions confirms the view that I.Z.S. should be used in those patients developing local sensitivity with the older insulins.

A high percentage of patients on two daily injections of soluble insulin or on injections of P.Z.I. and S.I. mixtures can be stabilized on I.Z.S., as has been demonstrated in this series. Nevertheless, in some patients such transfer is attended by the risk of a temporary and sometimes marked deterioration of the diabetic state, as has been noted above (see Table II), and similar instances have been recorded by Fitzgerald *et al.* (1954). Oakley (1953) noted poor control on I.Z.S. in some of his patients transferred from the older insulins. This risk can be reduced by making the change gradually if the total daily dose of the older insulins is a large one, this procedure entailing the separate injection of the older and newer insulins during the period of transfer. There is obviously a strong case to be made for a trial with the insulin zinc suspensions in patients on two daily injections of the older insulins, but patients well balanced on one daily injection of the older insulins could justifiably be left alone, bearing in mind the possibility of difficulties arising after transfer to I.Z.S. On the whole I believe that patients passing through a difficult phase on soluble insulin or soluble and protamine-zinc insulin mixtures should have control restored by increasing the dose of these insulins before attempting transfer to I.Z.S.

Comparison with globin insulin is difficult because of limited experience. The three patients in this series transferred from globin insulin to I.Z.S. were well controlled by the latter, two of them much better than they had been on globin insulin, but the reverse effect was noted by Murray and Wilson (1953) and Fitzgerald *et al.* in each of their cases.

Hallas-Møller *et al.* (1952) stated that patients difficult to control on I.Z.S. alone can generally be stabilized on mixtures of two of the three suspensions. Nabarro and Stowers (1953) found that some of their patients needed a higher proportion of I.Z.S. (crystalline) in the mixture. On the other hand, the type of case normally controlled by an S.I./P.Z.I. mixture of 2:1 or higher may well need more I.Z.S. (amorphous). In this series, four patients not well controlled by I.Z.S. alone were reasonably well stabilized by I.Z.S. mixtures. A small percentage of severe diabetics are best controlled on two or more daily injections of soluble insulin.

Summary

A series of 52 cases of diabetes mellitus were treated with insulin zinc suspension. All 16 new cases were satisfactorily stabilized on this preparation. Of the 36 patients transferred from treatment with older insulins, 26 were satisfactorily controlled by I.Z.S. alone, and 4 other cases reasonably well controlled by I.Z.S. mixtures. Six patients were restored to their previous insulin treatment because it had been more effective, and in some of them the diabetes had become markedly out of control whilst on I.Z.S.

I wish to thank Evans Medical Supplies for the insulin which they generously supplied for the earlier stages of this trial.

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The National Association for the Prevention of Tuberculosis has published a revised edition of *Help for the Tuberculous* (68 pages). It gives particulars of facilities available for tuberculous patients under the National Health Service and explains the provisions for the medico-social care of patients and their families. Sections on rehabilitation and future development in this field are also included. The booklet is published by the N.A.P.T. at Tavistock House North, Tavistock Square, London, W.C.1, price 5s.

SIMPLE CONDITIONS OF THE OESOPHAGUS SIMULATING CANCER

BY

R. H. FRANKLIN, F.R.C.S.

(From the Department of Surgery, Postgraduate Medical School of London, W.12)

When an elderly patient complains of dysphagia of recent onset suspicion is immediately aroused that the underlying cause is malignant, and further investigation usually confirms this suspicion. In recent years, however, an increasing number of patients are found to be suffering from what proves to be a simple condition. The onset of the dysphagia and the previous history of these patients usually give an indication that the cause may be benign, and at the present time strictures due to reflux oesophagitis are frequently diagnosed and treated.

In the cases described below the situation was somewhat different. In each the nature of the symptoms and the radiological appearances deceived experienced surgeons into making a confident diagnosis of cancer. Three of the patients were considered unsuitable for radical cancer surgery, and in every case the dysphagia was so severe that, left untreated, death would appear to have been inevitable. These four patients have come under my care within the last 12 months.

Case 1

In May, 1953, a man aged 69 was transferred from another hospital, where a diagnosis of carcinoma of the lower third of the oesophagus had been made. He gave a history of progressive dysphagia for twelve months and a loss of 2 st. (12.7 kg.) in weight over the same period. In January, 1953, he had had a perforated peptic ulcer which was treated by suture.

On admission to Hammersmith Hospital he was given a fortified liquid diet, but his swallowing gradually deteriorated, and it was necessary to carry out a gastrostomy on May 29. Following this his swallowing improved and a combination of mouth and gastrostomy feeding was instituted. The fact that he had had a perforated peptic ulcer raised the possibility of a simple cause for his dysphagia, but he was very kyphotic and it was thought unwise to attempt oesophagoscopy.

On June 16 exploration was made through a left abdomino-thoracic incision. The lower end of the thoracic oesophagus was grossly thickened, but the stomach appeared to be normal. The lumen of the oesophagus was opened to confirm the nature of the stricture and was found to be narrowed to a diameter of 2 mm., but there was no evidence of cancer. The lower third of the oesophagus and a large part of the lesser curvature of the stomach were excised and continuity was restored by anastomosing a loop of small bowel to the cut end of the oesophagus.

The patient made an uninterrupted recovery, and is now eating all types of food and gaining weight.

Subsequent histological examination of the oesophagus showed that the lumen would just admit a 2-mm. probe and the oesophageal wall at this point was 14 mm. thick, the greatest increase being in the submucosa.

The lumen in the section measured 3 by 2 mm. and had lost its epithelium, being lined by non-specific granulation tissue made up of young capillaries, fibroblasts, polymorphs, macrophages, and lymphocytes. Outside this layer and replacing the submucosa was a layer of collagen, 5 mm. thick, infiltrated with plasma cells, polymorphs, and eosinophils. The picture was that of a chronic non-specific oesophagitis with stricture formation. No evidence of malignancy was seen.

Case 2

A man aged 79 was admitted to hospital in August, 1953, with acute dysphagia for three days. There was no previous history of indigestion.

On examination he was very dehydrated and his blood pressure was 100/75. Barium swallow showed obstruction at the lower third of the oesophagus, probably malignant. *X*-ray examination of the chest showed a calcified aorta and emphysematous lungs. An electrocardiogram indicated possible ischaemic changes. In view of these findings oesophagoscopy was not undertaken.

A fortified liquid diet was given and on September 24 he was taught to swallow gum-elastic bougies. With this treatment his swallowing rapidly improved. He has continued to maintain his improvement, and it is probable that the cause of his dysphagia was a simple condition.

Case 3

A woman aged 84 was admitted in October, 1953. She had had epigastric pain for five months and regurgitation of solid food for three months. Her general health had always been remarkably good until the last few months, when she had been losing weight. A barium swallow and meal had been carried out at another hospital, where the condition was diagnosed as carcinoma of the fundus of the stomach, but in view of her age no treatment was considered practicable and she was sent home.

The increase in her dysphagia led to her being admitted to Hammersmith Hospital, where she was given a fortified liquid diet. After four days a fresh *x*-ray investigation was carried out and the condition was seen to be one of cardiospasm. In view of her age it was decided to pass a Hurst mercury bougie without carrying out a preliminary oesophagoscopy. The mercury bougie was introduced with ease and her swallowing rapidly improved. On discharge from hospital on November 6 she was eating a normal diet and gaining weight. At the time of writing she has had no further dysphagia.

Case 4

A man aged 79 was admitted in June, 1953, with a history of increasing dysphagia of 18 months' duration, and during this time he had periods of remission lasting as long as a month when food could be swallowed normally. During the week before admission he had almost complete dysphagia and found it very difficult to take even fluids.

On examination kyphosis was observed, but apart from his loss of weight there were no other abnormal physical signs. A barium swallow showed a short stricture just below the arch of the aorta, with some proximal dilatation. The stricture appeared to be simple in nature.

In view of his age and the presence of kyphosis, oesophagoscopy was considered to be dangerous, and a mercury bougie was introduced which passed through the stricture with unexpected ease. Following the passage of the bougie he was able to swallow normal food and was discharged on July 3, passing the bougie once a day. When seen on January 1, 1954, he was eating all kinds of food, including meat, and was swallowing his bougie once a week.

This case appears to be an example of simple spasm occurring in the middle of the oesophagus.

Summary and Conclusions

Four cases are described in which the symptoms and radiological signs have led to an erroneous diagnosis of cancer of the oesophagus.

In each case the experienced surgeon or radiologist who made the diagnosis was well aware of the possibility of a simple condition simulating cancer, but in spite of this was misled.

The mistake is likely to occur when confirmatory oesophagoscopy is contraindicated, and in such cases a second *x*-ray examination carried out after the patient has been restricted to a fortified liquid diet may be of help. In other cases it may prove necessary to carry out an exploration.

The possibility of a simple condition simulating carcinoma must be remembered in assessing the results of treatment by irradiation when it has not been possible to confirm the diagnosis by biopsy.

Medical Memoranda

A Case of Trichlorethylene Addiction

In view of the wide use of trichlorethylene ("trilene"), both in commerce and in medicine, the following description of a case of addiction is of interest. Similar cases have been described, though none, so far as I am aware, involving such medico-legal and psychiatric implications as in this case.

Trichlorethylene is a halogen hydrocarbon bearing the formula $CHCl.CCl_3$. It is subject to decomposition under the influence of heat or light, one of its breakdown products being dichloracetylene, a very volatile substance. The latter, when experimentally injected into rabbits, has produced encephalitis. When used for therapeutic purposes trichlorethylene is kept in brown stoppered bottles, or in sealed tins, in order to avoid the danger of decomposition. When used as an anaesthetic it should be coloured in order to distinguish it from chloroform. It would appear that smoking in the presence of trichlorethylene vapour encourages the inhalation of an irritant breakdown product of the drug.

Uses.—One of the commercial uses of trichlorethylene is as a dry-cleaning and degreasing agent. It is with the use of the commercial product that the present case arose. In its purified and stabilized form ("trilene") it is used as an anaesthetic for general surgery and as an analgesic in obstetrics. In ordinarily skilled hands it provides a safe method of induction. The drug has recently come into use in psychiatric clinics as an abreaction agent. The patient holds the mask himself and is told to breathe in. As soon as relaxation of the musculature occurs he is encouraged to try to recall his experiences. His reminiscences are vividly recounted, and he appears to be reliving many of the traumatic events in his life. Used in these ways, the drug is perfectly safe. Lastly, it is used, legitimately and safely, for sniffing in cases of trigeminal neuralgia, up to 4 ml. a day being the optimum quantity.

Psychosomatic Effects.—Apart from surgical anaesthesia, mention should be made of certain side-effects sometimes encountered, and also of the long-term results of excessive use or of use spread over long periods. Some of the cases of chronic poisoning with trichlorethylene in commercial undertakings may well have been attributable to impurities rather than to trichlorethylene itself. Symptoms have included giddiness, vomiting, optic neuritis, disturbances of sensation, and peripheral neuritis. After anaesthesia with trichlorethylene psychosomatic symptoms are sometimes reported, though they are usually slight and evanescent. In the main, they are of the nature of headache, nausea, vomiting, and mental confusional states. Amnesia is said to follow its use in some 20% of cases in which it was self-administered in obstetrics. Addicts who had been using from 120 to 180 ml. a day showed mental changes, mainly in the direction of hypomanic phases and disorientation, but these cleared up rapidly when the habit was broken off. Tremor, nausea, emotional lability, mild delirium, sometimes with frightening hallucinations, have been reported, and have been attributed to breakdown products, perhaps phosgene.

CASE REPORT

The patient, a young man aged 25, lived alone with his mother on terms which, in the opinion of those who knew both well, were happy. His parents separated during his very early childhood. The history of his addiction to anaesthetics generally is briefly as follows. At the age of 18 he held the post of orderly in a hospital, where his duties included the care and management of the theatre trolley. He became obsessed with the speculation of "trying out by way of experiment, and just to see what it felt like," one of the anaesthetics, his first choice falling on the nitrous oxide apparatus. After a while he switched over to ethyl chloride, because this had the double advantage of being put up in a spray bottle and needing only a handkerchief for its administration. Of this he took "a very large quantity, and the sensation soon became a habit." But once more he tired of its action and turned his attention to pure ether. He had by now reached the stage of craving for "the sensation of sleep and oblivion," and had begun to take the drug home with him in order to be able to use it in bed. This went on for more than two years, and it appears that on many occasions trouble had arisen between his mother and himself over the use of what she had described as "suicidal drugs."

It was about this time that he left the hospital and entered a works, where his job consisted of cleaning electrical equipment with semi-crude trichlorethylene. For a little while he did not miss the anaesthetics too much. But presently the old compulsion made itself felt again, and this time he turned to trichlorethylene, handy, accessible, and copious as it was. He quickly discovered that its action was very much like that of ethyl chloride (for his specific purpose, that is), and he soon established the habit of soaking his handkerchief with it at any odd time of the day, but more especially at bedtime. He would fill a pint—and later a quart—bottle with it and take it home. At bedtime he would soak a cloth with the trichlorethylene, put it over his nose and mouth, and then draw the bedclothes over his head, thereby providing himself with a good imitation of the closed method of induction. Eventually he would fall sound asleep. In the morning, however, he felt depressed and his limbs felt "just as if they were covered with a rubber glove; all my sensations were blunted."

This addiction had lasted for some three years or more, when one night, after what must have been a regular trichlorethylene debauch, he experienced a state of mind which he described as a "queer sort of elation; everything seemed clear, but strange; I felt highly amused at nothing in particular, and I wanted to burst out laughing." This was followed the next morning by a depressive episode, coupled with blunted skin sensations. He returned to his bedroom for more trichlorethylene. On coming downstairs again he picked up a kind of heavy stick in the scullery and viciously beat his mother with it. She died of her injuries within a few hours.

Thirty minutes later he was found, disoriented, in a street near by. His behaviour was then so violent that the police were obliged to strap him down to the ambulance couch. He was, however, aware of what he had done and kept repeating that he had killed his mother. Some three hours after his maniacal outburst he had calmed down and was able to give a much-restricted account of what had happened that morning. It should be mentioned that at that time he was doing night duty and that his sleep induction would therefore take place somewhere about eight in the morning.

The prosecution accepted a plea of manslaughter whilst under the influence of a narcotic drug.

COMMENT

As this man had indulged in trichlorethylene inhalations for three years without precipitating a clinically ascertainable psychosis, it must be assumed that during the few hours

before the onslaught on his mother he must have used an uncommonly large amount of the drug. (There were, in effect, two empty pint bottles on the kitchen table, both of which had contained trichlorethylene.) Moreover, the chemical purity of this particular brand was, clearly and expectedly, below the standard set for medical use. The patient gave a history of epileptiform attacks in childhood, and was said to have been emotionally unstable. Whatever interpretation we put on a scanty history of this sort we shall certainly be right in assuming, on the grounds of a five-year addiction to anaesthetic drugs, the presence of some constitutional psychopathy, vague though one admits this to be. Again, he was subject to mood swings, though they were invariably on the depressive side. During such moods he was given to criticizing his mother, though not in a very robust way, for her attempts to interfere with his drug-taking, and also for what he called her extravagances with his wages. It is more than probable that during his brief but acute intoxication his hitherto repressed paranoid feelings towards his mother were given uninhibited rein and, in the setting of reduced awareness, he performed his retributive act. The effect of the overdose of trichlorethylene was, in fact, of the nature of a psychological abreaction, during which the patient enacted the content of his paranoid experiences with regard to his mother, for whom his feelings must at all times have been ambivalent.

WM. A. O'CONNOR, L.M.S.S.A., D.P.M.,
Medical Superintendent, Ashwood House, Kingswinford, Staffs.

Negative-pressure Drainage in Radical Mastectomy

Collections of fluid under the flaps after radical mastectomy cause an annoying delay in the healing of the wound and a prolonged stay in a costly hospital bed. In my opinion the fluid gathers in dead spaces which are produced by air trapped beneath the skin. For this reason I have been using negative-pressure drainage, with most gratifying results.

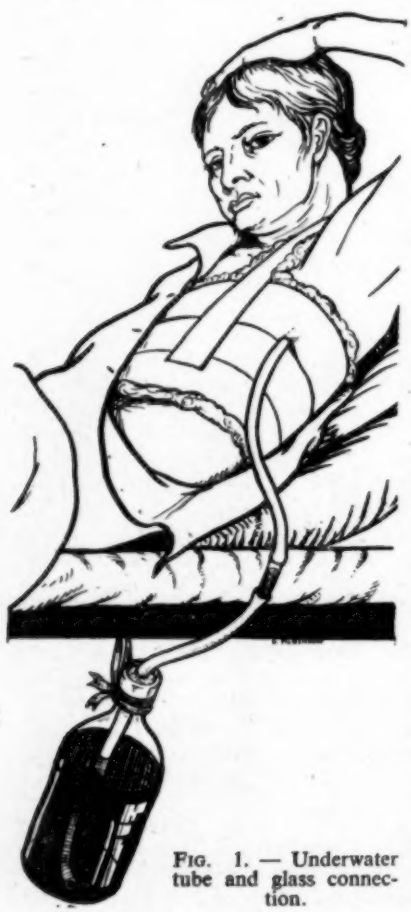

FIG. 1. — Underwater tube and glass connection.

METHOD

Before suture of the wound, a 2½–3 ft. (76–90 cm.) length of rubber tubing with a lumen as wide as a cigarette is introduced through a stab wound in the lateral flap at the anterior border of the latissimus dorsi a handbreadth below the armpit, the low site being important, as wounds in axillary skin do not heal well. The tube is anchored to the skin by a stout suture. The wound is then stitched, and on completion the skin is pressed to the chest wall with both hands in order to express the air via the tube, which is then plugged with a spigot by the assistant. On the patient's return to the ward the tube is connected to an under-water tube and glass connexion as shown in Fig. 1. Air is next aspirated from the tubing by needle and syringe until the water rises into the connexion. Removal of air is repeated daily in order to restore the water to this level. The tube is removed on the fifth day, when the first and only dressing of the wound is done. Sutures are taken out on the eleventh and twelfth days (Fig. 2), when full arm movements are always possible.

FIG. 2.—Sutures ready to be taken out at eleventh and twelfth days.

Complementary Points in Operative Technique.—(1) The incision is made to run vertically from the coracoid process towards the ninth costal cartilage, as recommended by Marshall (1951). This carries the wound away from the anterior fold of the axilla, where tethering and contracture so often occur in the more traditional incision. In the case of neoplasms near the sternum the wound will unavoidably deviate towards the midline. (2) The breast and pectorales are removed first, the contents of the axilla second (Marshall, 1951), when oozing beneath the flaps will be found to have stopped. (3) The wound is sutured with vertical mattress sutures at ½-in. (1.3-cm.) intervals in order to obtain epidermal coaptation and thus sound primary union. (4) The minimum of elastic adhesive bandage and wool dressing is employed (Fig. 1), so that the patient is reasonably comfortable and has unrestricted movement of the shoulder from the moment of return to consciousness.

Advantages Claimed for Drainage System.—The patient is spared repeated changes of soaking dressings; pooling of serum under the flaps is avoided; full movement of the shoulder is possible from the first day; and sound primary union is obtained, enabling discharge from hospital in two weeks from the date of operation.

Negative-pressure drainage of the radical mastectomy wound has been in regular use in this surgical unit for the past two years, and it has transformed the convalescence of these patients.

I am grateful to Mr. J. Scholefield for permission to publish, to Miss S. Robinson for the drawing, and to Mr. Vinten for the photograph.

GORDON F. CASSIE, F.R.C.S.,
West Middlesex Hospital, Isleworth.

REFERENCE

Marshall, Samuel F. (1951). In *Surgical Practice of the Lahey Clinic*, p. 606. Saunders, London.

The Division of Occupational Health of the U.S. Public Health Service has published a *Bibliography of Occupational Health* (Government Printing Office, Washington, 25, price 35 cents). This bibliography of 110 pages presents a comprehensive listing of nearly 2,000 papers in journals, reports, and other publications emanating from the Public Health Service from 1909–53. A full subject index is included.

Reviews

WHY BE A DOCTOR?

Why we became Doctors. Edited by Noah D. Fabricant, M.D. (Pp. 182. $3.75.) New York: Grune and Stratton, Inc. 1954.

Fifty doctors here give their reasons for studying medicine. Nine were directly approached by the editor, the others published their reasons in autobiographies. We found the extracts from the published books more interesting. Most of the doctors are Americans, but six lived in Britain, and we were glad to find the veteran Alfred Cox among that distinguished number.

Have you, reader, ever stopped to think exactly why you studied medicine? If so, you will understand that motives are often mixed and circumstances frequently compel. Nevertheless the reasons here adduced furnish food for thought. Frequently the example of another member of the family, usually the father, was the apparent cause. Difficulties seldom deterred. When the father of Lewis Tryon died the widowed mother "would make any kind of sacrifices necessary to make me the sixth generation representative of the Doctor Tryon line." Ronald Ross entered medicine to please his father. Some entered a medical career because they saw the doctor was of some importance or of obvious use to the community. Franklin Martin wished to avoid the drudgery of manual labour. James Herrick wished to be his own master. The disturbing influence exercised by the other sex forced upon Elizabeth Blackwell "the necessity of devoting herself to some absorbing occupation" and she chose medicine. Havelock Ellis and Freud made their choice suddenly, the former on reading the life of James Hinton and the latter on hearing Goethe's essay on Nature read aloud. Somerset Maugham was not particularly interested in the medical profession, but it was decided that he should become a doctor; his final judgment was that he did "not know a better training for a writer than to spend some years in the medical profession"! Readers of the *Citadel* may not be surprised to learn that Dr. A. J. Cronin went in for medicine because "it was safe and practical."

Strange to say, few of the 50 lay much stress upon medicine as a vocation. Yet Carlos de Vighne writes of the time when someone asked him why he wished to study medicine: "How could I tell him that what I wanted above all was to be wanted?" The outstanding example of dedication is that of Albert Schweitzer: "This new form of activity I could not represent to myself as being talking about the religion of love, but only as an actual putting it into practice." We believe that many doctors who have a true vocation to medicine and a wish to help suffering humanity do not like to talk about their deeper convictions.

ZACHARY COPE.

BEHAVIOUR DISORDERS OF CHILDREN

Clinical Management of Behavior Disorders in Children. By Harry Bakwin, M.D., and Ruth Morris Bakwin, M.D. (Pp. 495; illustrated. 50s.) Philadelphia and London: W. B. Saunders Co. 1953.

The name Bakwin is associated in the minds of paediatricians and child psychiatrists with a very important piece of work, "Loneliness in Infants" (*Amer. J. Dis. Child.*, 1942, **63**, 30). Here was clearly shown the need of infants for personal attention when in hospital and also the physical deterioration that follows impersonal management. This publication of Bakwin provided an important link between psychology and physical paediatrics and is partly responsible for the agreement which is to be found at the present time among all those who care for infants and small children that impersonal or mechanical management is disastrous. The reader is therefore excited to find a large-scale study of infants and children by the same author.

This book covers a very wide field and contains a great deal of wisdom on the management of infants and children of all ages and in all sorts of conditions. The emotional needs of various types of physically ill children are described and the various symptoms of emotional disturbance are discussed one by one. It would indeed be a pleasure to find that this book has throughout an importance comparable to that of the paper "Loneliness in Infants." However, we cannot say that. It is difficult to see what public the authors are addressing. For paediatricians who have but little time for psychology the book contains a valuable statement on almost every symptom and group of symptoms, but the statement is descriptive and not of a penetrating kind. Certainly there are intelligent parents who would like to have this book on their shelves, to use it as a kind of encyclopaedia which can be relied on to be informative, and to give wise advice about psychological symptoms and the psychological side of physical illnesses. For the child psychiatrist and for the psycho-analyst, however, this book seems to lack the essential structure of a psychological theory. There is in this book so much work based truly on clinical experience that it seems uncharitable to complain, but unfortunately psycho-analysis can no longer be avoided by those who write on psychology. The book is beautifully produced, and at the end of each section there is a useful bibliography.

D. W. WINNICOTT.

ACUTE TUBULAR NECROSIS

Acute Anuria: A Study Based on Renal Function Tests and Aspiration Biopsy of the Kidney. By Claus Brun. (Pp. 215; 62 figures. Dan. kr. 30.) Copenhagen: Einar Munksgaard. 1954.

This very readable monograph presents a historical and experimental study of the condition now usually known in Britain as acute tubular necrosis. The new data presented are derived from thirty-two patients with acute renal failure from various causes such as sulphonamide therapy, enteritis, hepato-renal syndrome, incompatible blood transfusion, and poisoning by various drugs. An element of shock was present in many of these cases, and the author suggests that renal ischaemia is a major aetiological factor in most instances.

Observations were made on a number of renal-function tests including urea, creatinine, inulin, and *para*-amino hippuric acid clearance. The average rise in serum urea concentration was 50 mg./100 ml. per day. The 24-hour creatinine clearance was found to be particularly useful. With the clearance tests it was demonstrated that ultrafiltration in the glomeruli returned sooner than tubular secretion. In cases which recovered the function tests returned to normal values within twelve months. Severe anaemia was frequently present during the recovery period.

The histological changes in the kidney were investigated by post-mortem observations in some cases and in others by puncture biopsy of the kidney during life. The details of this procedure, together with a discussion of the risks involved, are given: 164 attempts were made on 133 patients, sufficient tissue for histological examination being obtained in only 66. No complications were encountered apart from transient haematuria following the procedure. The histology showed mainly normal glomeruli and blood vessels with a variety of tubular changes, most of which were not localized to any particular part of the tubule. In a few cases the changes were inconspicuous in spite of severe functional damage.

This work can be recommended as a good general account of the condition which serves to confirm most of the accepted ideas on the subject, and the main novelty lies in the biopsy data. This comparatively new puncture biopsy technique is a method which will probably commend itself as a research tool to others interested in this subject.

N. F. MACLAGAN.

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TREATMENT OF LEUKAEMIA

The rapid advances made by haematology in recent years have thrown into sharp relief the intractability of leukaemia. Our diagnostic methods here become more precise, but we have no knowledge of its cause and its issue remains inevitably fatal. Although still a rare disease, its incidence is increasing, and, by often selecting its victims from among the young and healthy, it causes an amount of suffering and distress out of proportion to its frequency. The leukaemic process must be regarded as, in the broadest sense, neoplastic; it is a cellular proliferation, apparently purposeless, without evident cause, and ultimately irreversible. It differs from most other tumours in being multicentric or systematized, but in a biological sense it is as malignant as any other neoplasm. These considerations throw no light on its causation; they shroud it in a pall of mystery which envelops the cause of all cancers.

In human leukaemia the aetiological importance of only one factor is established, and this is radiant energy. The disease is eight times more common in radiologists[1] than in other members of the medical profession, and the Japanese have reported its incidence in survivors of the atomic-bomb explosion at Hiroshima to be eight times that of the general population of Japan.[2] It may be doubted whether comparison between human and animal leukaemia is justifiable, but in some varieties of the latter the cause is better understood. Acute erythromyelosis of fowls was shown to be due to a virus as long ago as 1908.[3] Artificial inbreeding of mice has yielded the Ak strain, of which 70% develop lymphatic leukaemia at the age of 7–10 months, providing clear evidence, it was believed, of a hereditary predisposition. Gross[4] has cast doubt on the validity of this assumption by showing that inoculation of a cell-free extract of leukaemic Ak mouse tissue, if made before the recipient is 24 hours old, can transmit the disease to mice of a strain in which the incidence of spontaneous leukaemia is only 0.5%. Of these animals, 81% developed leukaemia at about the age of 10 months; if the inoculation was made when the animal was 7 days old, the disease appeared in none. In those animals affected in middle age by leukaemia the disease was transmitted to the offspring in a high proportion. He concluded that the leukaemia of Ak mice was due to a filtrable agent transmitted from one generation to the next *in utero* and remaining dormant until the animal had reached middle age. Heredity does not appear to play a dominant part in the human disease. Videbaek[5] found the familial incidence to be 8% and concluded that an inherited predisposition existed. The application of Gross's observations, if they can be confirmed, to human leukaemia is not obvious.

Ignorance of causation has limited treatment to the empirical. All the methods employed discourage cellular proliferation by a direct action upon the proliferating cell and not because they control the fundamental cause. With the exceptions of cortisone and A.C.T.H., all the agents effective in leukaemia are injurious to normal haemopoietic tissue, but, in the doses given, exert in some degree a selective action on pathological proliferations of its cells. The methods at our disposal are radiotherapy and chemotherapy. Irradiation in the form of *x*-ray therapy has been the conventional treatment of chronic leukaemia for half a century; in chronic myeloid leukaemia it still maintains its position. The radioactive isotopes have proved disappointing, except in polycythaemia rubra vera.

Since the war the focus of interest has shifted to chemotherapy. Arsenic and benzene have been used for many years, but it was the introduction of the nitrogen mustards which provided the stimulus to the researches of the past four years. Since 1945 a variety of cytotoxic agents have been developed capable of affecting leukaemic proliferations, albeit temporarily. This class of drug is of value only in the more chronic types of the disease, and the various substances employed often have a surprising specificity. Thus urethane will control chronic myeloid leukaemia and, in lesser degree, myelomatosis; triethylene melamine will procure remission in chronic lymphatic leukaemia; and "myleran" (1:4-dimethanesulphonyloxybutane) in chronic myeloid leukaemia. The other group of chemotherapeutic agents have been developed along a different path and their value lies in their action on the acute leukaemias. These are the antimetabolites, which exert their effect by replacing a metabolite in its particular enzyme system and thus depriving the rapidly dividing cells of an essential nutrient. The folic-acid antagonists were the first of this order. Leukaemic cells contain five times more folinic acid—the active derivative of folic acid—than normal leukocytes,[6] and

[1] March, H. C., *Amer. J. med. Sci.*, 1950, **220**, 282.
[2] Amano, S., *Proc. internal Congress Haematol.*, 1952, Mar del Plata, Argentina.
[3] Ellermann, V., *The Leucosis of Fowls and Leucaemia Problems*, 1921, London, Glydendal.
[4] *Ann. N.Y. Acad. Sci.*, 1952, **54**, 1184. *Cancer*, 1953, **6**, 153.
[5] *Heredity in Human Leukaemia and its Relation to Cancer*, 1947. London, Lewis & Co.
[6] Swendsied, M. E., *et al.*, *Cancer Res.*, 1951, **11**, 864.
[7] Burchenal, J. H., *et al.*, *Blood*, 1953, **8**, 965.
[8] *New Engl. J. Med.*, 1954, **250**, 131.

it is reasonable to suppose that this indicates their extravagant metabolic requirements and would make them more susceptible to deficiency induced by a folic-acid antagonist. Aminopterin and amethopterin, the best-known members of this group, have shown their ability to induce temporary remission in as many as 50% of cases of acute lymphatic leukaemia in children. They are of little value in other forms of leukaemia and of still less in the disease occurring in adults. More recently attention has turned to purine antagonists, and one of these, 6-mercaptopurine, has been found to procure remission in a high proportion of acute lymphatic leukaemias of childhood and occasionally even in adults.[7] It must be stressed that the remissions obtained with antimetabolites are usually short-lived, often incomplete, and occur almost only in children. Second, and sometimes third, remissions have been obtained, but the disease eventually becomes resistant.

Cortisone and A.C.T.H. were first used in leukaemia because of their well-known effects on lymphoid tissue. They have proved capable of procuring remission in the acute types of the disease, particularly in the lymphatic variety and particularly in children. The effect may be of dramatic rapidity, but is seldom of more than a few weeks' duration. Some workers have found that the combination of A.C.T.H. or cortisone with a folic-acid antagonist gives better results than either alone, and Dameshek[8] has claimed complete remission in 25 of 26 consecutive cases of acute lymphatic leukaemia in children using these two agents simultaneously.

Progress in the last few years has been therefore largely limited to the treatment of acute leukaemia. The critical may object that the progress is more apparent than real, for the disease remains as surely fatal as in the past. Nevertheless a gleam of light may be discerned, for it has been proved that the cellular proliferation of acute leukaemia can be halted for a while, and for a while the bone marrow can be restored to normal and the patient to health. Such temporary improvement permits the hope that one day permanent control will be possible.

ARE ACCIDENTS INEVITABLE?

Nowadays anyone who is unfortunate enough to hit his thumb with a hammer twice in one Saturday afternoon, or to carry away the front gate-post on successive days, is liable to be dubbed "accident-prone" by his or her critical relatives. As with many phrases which have come into common use, "accident-proneness" was originally introduced in a special sense which is worth a little trouble to understand.

In 1919 Greenwood and Woods[1] made a study of minor accidents suffered by munition workers, all of whom were engaged on the same operation. Over a period of time it was observed that some of the workers were unscathed, some were injured once, some twice, and some more often. This might have occurred merely by chance, some workers being less fortunate than others. But when the point was tested[1 2] this explanation was found to be unacceptable: more workers had large numbers of accidents, and more had no accidents at all, than if all had been equally likely to be injured. Greenwood and Woods therefore suggested (among other explanations) that individuals might differ in their liability to incur accidents. It was well known that the nature of the work, the adequacy of the lighting and the temperature, and the length of the working day all affected accident liability. However, because Greenwood and Woods had attempted to choose groups of workers among whom these influences would be as uniform as possible, the important suggestion emerged from their analyses that, apart from these external influences affecting the group, there appeared to be individual differences in accident susceptibility. That is, the occurrence of an accident seemed not to be purely accidental but to involve a personal element.

This concept of different individual susceptibilities to accident under the same external conditions was christened "accident-proneness" by Farmer and Chambers.[3] Despite inadequate evidence, it gradually became widely believed that people who were unduly susceptible to accidents in one set of circumstances would also be unduly susceptible at another time in quite different circumstances, and that some people were inherently "accident-prone" and some were not. These unjustified extensions of the original concept, and some of the more extravagant claims made on these lines, have been well reviewed by Adelstein.[4]

Apart from these wider considerations, it is clearly desirable, if possible, to identify in advance those individuals who are particularly likely to injure themselves—and others—in given industrial circumstances, in order to employ them on less hazardous work. Much effort has been expended[3 5 6 7] in attempting to distinguish, by means of psychological tests, individuals who are potentially susceptible to accidents, but these attempts have been only partially successful. As Greenwood[8] wrote, "So far no test, or

[1] *Report of Industrial Fatigue Research Board*, London, 1919, No. 4.
[2] Greenwood, M., and Yule, G. U., *J. roy. statist. Soc.*, 1920, **83**, 255.
[3] *Report of Industrial Fatigue Research Board*, London, 1926, No. 38.
[4] *J. roy. statist. Soc.*, 1952, **115**, 354.
[5] Farmer, E., and Chambers, E. G., *Rep. industr. Hlth. Res. Bd., Lond.*, 1929, No. 55.
[6] —— *et al.*, ibid., 1933, No. 68.
[7] —— and Chambers, E. G., ibid., 1939, No. 84.
[8] *Biometrika*, 1950, **37**, 24.
[9] *Brit. J. industr. Med.*, 1954, **11**, 126.

battery of tests, has been found which would exclude the highly accident-prone *without* excluding a considerable proportion . . . who are not specially 'bad risks.'"

A valuable advance in the understanding of individual accident susceptibility has now been made by Whitfield.[9] He has analysed information on underground "compensation" accidents in relation to individual working records at a colliery in the Nottinghamshire coalfield employing approximately 2,000 men. The data were collected from July, 1944, to December, 1946, inclusive. By classifying the accidents and the shifts worked according to occupation and place of work it was possible to calculate the accident risk per shift for moderately homogeneous working groups. From these figures an expected total of accidents could be computed for each miner, and compared with the actual number experienced. The results indicated clearly that there were individual differences in accident susceptibility among coalminers which persisted for several years, but that these were not readily attributable to the age of the worker nor to inherited tendencies. A detailed investigation was therefore made of three small samples of the miners. One was composed of men who had experienced many more accidents than were expected—the accident-prone group. Each individual was then matched, by age and normal mining occupation, with two others who had experienced, respectively, about as many accidents as were expected, and fewer accidents than were expected. Thirty-two of these triads were examined by interview and a series of tests; the panel which tested each triad did not know which member belonged to which accident category. Among the tests used were measurements of visual and auditory acuities, performance tests of perceptual, cognitive, and memory functions, and tests of motor control and co-ordination.

It was found that the younger accident-prone men were markedly deficient in the perceptual-cognitive tests, while the older accident-prone men were markedly deficient in motor control and co-ordination. Whitfield suggests that the younger accident-prone man is unable to appreciate the demands of a hazardous situation or to decide what response should be made, although capable of making the response, whereas the older accident-prone individual fails to produce an adequate response, even though the hazard has been perceived and an appropriate course of action initiated. If this is so, it is easy to understand why those naturally deficient in motor ability when young should become accident-prone as their motor ability slowly deteriorates with age. It is not so easy to see why young accident-prone miners should apparently cease to be so. Some, presumably, die young; the rest perhaps leave the industry for less hazardous occupations, or, while remaining in coalmining, adjust themselves to a reduced level of activity.

It is clearly important that confirmation of these hypotheses, based as they are on small numbers, should be sought both inside and outside the coalmining industry. Coalmining, although notoriously hazardous, is not the only dangerous occupation. Moreover, many accidents occur outside the mine or factory. For example, the unabating toll of deaths from road accidents illustrates the desperate need for a clearer understanding of the personal factors responsible. If the same general hypotheses are found to hold for motor-car drivers, or for that matter pedestrians, as for miners, valuable progress will have been made towards the elimination of at least two causes of death which are rightly the subject of so much public concern.

STRESS AND STROKES

The close relationship between emotional experience and transient fluctuation of blood pressure and pulse rate is an old and well-known observation, and "of all pyschosomatic interrelationships . . . subjected to the earliest and most extensive studies."[1] Hence cardiovascular and cerebrovascular accidents have long been linked with "emotional experience . . . trivial though the incident be."[2] John Hunter said, "My life is in the hands of any rascal who chooses to annoy and tease me."[3]

Alkan's[4] theory that "functional angiospasm is either the sole cause or at least an integral component in the production of the apoplectic insult" has recently been propounded afresh by Ecker[5] from a study of 20 cases of "both nontraumatic intracranial hemorrhage and sudden hemiparesis." Byrom[6] suggests that arterial spasm as "a direct local response to the physical strain of excessive intra-arterial tension" also accounts for "acute hypertensive encephalopathy and the various clinical and pathological characters of malignant hypertension." Most of Ecker's patients were under the age of 50 and were found to have been undergoing some "special emotional stress" immediately preceding the onset of symptoms. Fifteen of the patients were shown by angiography to have "an excessive tendency to arterial contraction," which is taken as "one of the bodily expressions of the emotional disturbance" and responsible for the "stroke." Ecker postulates that this disturbed vasomotility resulting from "long-standing

[1] Dunbar, F., *Emotions and Bodily Changes*. New York. 1946.
[2] Wilson, S. A. K., *Neurology*, Vol. 2. London. 1940.
[3] Paget, S., *John Hunter*. London. 1897.
[4] *Anatomische Organkrankheiten aus seelischer Ursache*. Stuttgart. 1930.
[5] *Ann. intern. Med.*, 1954, **40**, 49.
[6] *Lancet*, 1954, **2**, 20.
[7] Schneider, R. A., and Zangari, V. M., *Psychosom. Med.*, 1951, **13**, 289.
[8] *Modern Trends in Dermatology*. London. 1954.
[9] Landis, C., and Gullette, R., *J. Comp. Psychol.*, 1925, **5**, 221.
[10] Scott, J. C., ibid., 1930, **10**, 97.
[11] Gillespie, R. D., *J. Physiol. (Lond.)*, 1923–4, **58**, 425.
[12] Macalpine, I., *Brit. J. Derm.*, 1953, **65**, 177.

progressive difficulty in settling emotional problems" leads to anoxia in the cerebral tissues, with resultant damage to them as well as to capillaries. In this way thrombosis, infarction, and haemorrhage are thought to be produced. An alternative explanation in younger patients in the absence of arteriosclerosis would be that a congenital weak spot gives way "as a sequel to altered vascular equilibrium induced by excitement."[2] Possibly changes in blood chemistry accompanying strong emotion may also tend to increase liability to haemorrhage.[7]

Whichever the ultimate mechanism, Ecker confirms general knowledge that emotional factors may in predisposed subjects precipitate a cerebral vascular accident, just as they may lead to coronary occlusion or perforation of peptic ulcer. Unfortunately the scope of his "personal histories" does not allow further or more definite conclusions to be drawn, and he embarks on the quicksands of personality assessment in psychosomatic illness in general, committing all the errors convincingly criticized by Macalpine.[8] Even if some abnormalities were demonstrated in the mental life of patients subject to cerebral vascular accident, these might equally as well be the result as the cause of the condition of the cerebral blood vessels. Moodiness, irritability, and emotional instability are well-recognized early manifestations of organic cerebral disease. They might also lead to the outburst that causes rupture of a blood vessel already the seat of congenital or acquired abnormality. Further, there is no correlation between the degree of emotion as reported introspectively or retrospectively and the degree of blood pressure or angiospastic change.[9] It is even doubtful whether anger and fear have characteristic vascular reactions.[10 11]

It is a strange commentary on psychiatric research to-day that, while psychiatric journals are embellished with articles on anaesthesiology, neurosurgery, and biochemistry, medical and surgical journals are increasingly devoted to psychological factors in disease. While Ecker, a neurosurgeon, pleads for more detailed personal histories by physicians and surgeons to bring out the psychiatric aspects of organic illnesses, many psychiatrists are searching for pathological lesions in mental disease, and treat their patients largely by physical methods. Emotional problems are encountered by everyone throughout life, and most of us could describe some recent emotional stress. It is therefore too easy and apt to be misleading to implicate psychological factors in the aetiology of diseases which are not yet fully understood. On the other hand, detailed psychological study of individual patients[12] may in doubtful cases be expected in the long run to advance both psychiatry and medicine.

THE LONDON SMOG DISASTER

About 4,000 people died as a direct result of the smog that covered London in December, 1952, but the exact cause of death remains unknown. Another report[1] on the disaster, published this week and compiled by an anonymous committee of Civil Servants and advisers appointed by the Ministry of Health, comes to the conclusion that the irritants mainly responsible for the deaths were "probably those derived from the combustion of coal and its products and their lethal effects were almost wholly exercised in persons already suffering from chronic respiratory or cardiovascular disorders." A careful review of all the evidence available has enabled the committee to add only very little to previous reports on the subject,[2-4] and the problem still remains of why that particular fog was so unusually deadly in comparison with the ordinary "pea-soupers" that cause much discomfort but not a startling rise in the death rate.

The post-mortem examination of patients who died during the smog provides the most important new data, though they are—no doubt of necessity—rather meagre. Dr. Bernard Lennox, of the London Postgraduate Medical School, studied sections of eight lungs from one of the public mortuaries and found "consistent changes in the mucosa of the larger bronchi in all eight lungs." The epithelium had been largely shed, an appearance that was probably a genuine pathological change, though artifact could not be wholly discounted. There was no necrosis such as is seen in most cases of influenza. There was an intense capillary engorgement confined to the immediate subepithelial layer and accompanied by a light cellular infiltrate of leucocytes. Finally, there were indications of the production of mucin in excessive quantities. While the changes were slight, Dr. Lennox found them to be "strikingly constant." A chemical examination by the Government Chemist, including spectrographic tests for trace elements, failed to show any significant difference between the mineral content of the lungs from three victims of the smog and that of a control lung. Special tests of lung material for the presence of the influenza viruses confirmed that they played no significant part in causing the deaths. The evidence of mortality collected at the General Register Office[2] confirmed the clinical evidence, discussed in these columns,[5] that it was mainly adults aged 45 and over who were affected, though mortality of infants under 1 year old also rose. The cases were chiefly seen as bronchopneumonia or severe bronchitis, and death certificates with such diagnoses showed much the greatest increase in frequency during and immediately after the smog.

As the Interim Report on Air Pollution[3] pointed out, the most likely noxious irritants in the fog were oxides of sulphur and particles of tarry matter, but such further study of the problem as has been possible adds nothing positive to the report's conclusion that there is no evidence "to enable us to identify with any certainty the pollutants and the combination thereof which were responsible for the particularly harmful nature" of the 1952 smog. Here as elsewhere in the problem posed by this disaster the occasion for studying it adequately was gone before the need became apparent. So vast is the

[1] *Mortality and Morbidity During the London Fog of December, 1952.* Reports on Public Health and Medical Subjects, 1953, No. 95, H.M.S.O., London, 2s. 6d.
[2] Logan, W. P. D., *Lancet*, 1953, 1, 336.
[3] *Interim Report*, Committee on Air Pollution, 1953, H.M.S.O.
[4] Wilkins, E. T., Air Pollution and the London Fog of December, 1952, read before the Royal Sanitary Institute, London, 1953.
[5] *British Medical Journal*, 1953, 1, 321.
[6] *The Menace of Air Pollution*, P.E.P. Planning, Vol. 20, No. 369.

Metropolis that an abnormal death roll even of this magnitude left the citizens unaware of its occurrence until the death certificates were analysed. Clearly there is a need for research plans as well as preventive measures to be devised and held ready for the future lest the opportunity for study should slip by again. Meanwhile, the prevention of smoke pollution remains an urgent matter, and it receives some useful publicity from P.E.P.[6] this week; for, though the chances are against London's again experiencing for many years yet the conjunction of climatic events that causes such a deadly fog, the smoke-polluted air hanging about its streets in winter must be injurious, albeit insidiously.

VOLUNTARY EFFORT IN HOSPITAL WORK

It would be idle to pretend that what has happened to the hospitals of this country during the last six years has not gone far to quench the voluntary spirit. The King Edward's Hospital Fund for London now derives only one-tenth of its ordinary income from subscriptions and donations; nine-tenths is income from investments which are a legacy of former benevolence dating back to Edwardian times. It is true that the Fund has never aimed at a high subscription income, having refrained from active competition with hospitals in the search for subscribers; but although a number of staunch supporters, headed by the Queen, still maintain their subscriptions the list has diminished materially. But the voluntary spirit is not easily extinguished, and the report of the Fund for 1953 testifies to a notable resurgence of voluntary effort in hospital work, with the formation of many new leagues of hospital friends. Moreover, the tradition that the hospital is the best of all ultimate destinations for a legacy is by no means outworn, and, if there is hesitation now to bequeath to an individual hospital, the Fund offers an obvious recourse, because the testator knows that the money will be used in the best possible way for the benefit of patients.

Grants have been made by the Fund during the past year to a number of improvement schemes, from £12,000 for the rehabilitation of one floor of the geriatric unit at West Middlesex Hospital to £50 for putting in a new gas cooker at a convalescent home at Broadstairs. The projects have included such things as a new cerebral palsy centre at a children's hospital, the renovation of a villa for a nurse-training school, and the provision of gardens, verandahs, wireless equipment, diet kitchens, and the like at a hundred other places. One of the special activities of the Fund is the running of London's well-known emergency bed service. In addition to its immediate purpose this serves as a seasonal index of the variations in acute sickness in the London area. It was found that during November and December of last year a surprisingly large number of applications were received for the admission to hospital of babies and very young children suffering from respiratory disease. So marked was the incidence that the Ministry of Health was informed, and it was found that nearly all the major cities in England showed a similar increase. There seems to be a tendency for "epidemics" of respiratory trouble to strike the very young before the middle-aged and elderly. An attempt has been made to correlate the rise and fall in illness with weather conditions, but, except that illness tends to increase during or very shortly after spells of low temperature and fog, no day-to-day relationship has been established.

The Fund also supports convalescent and recovery homes, many of which would be closed were it not for its aid in the background. It encourages nurse recruitment and training. Its catering service is one of its most useful activities, and includes the planning of kitchens, advice on food preparation, investigation of food costs, and arrangement of courses for catering officers. Of the twelve homes for the aged sick to be set up under a scheme inaugurated in 1949, the tenth is being opened this year. One of the benefits of the scheme is that the doctors concerned with the homes can reassure friends and relatives to whom the patients go on discharge that they are really fit enough to live a normal life and will have somewhere to go should their health fail again. Over 80% of the patients are in the homes for less than six months.

SPONDYLOLISTHESIS

Spondylolisthesis is one of the many disorders which cause low back pain. It is not common, but Colonna,[1] reviewing 201 cases, found the frequency to be 1.2% of all the patients treated in an orthopaedic clinic in Philadelphia over a ten-year period. The condition develops from a structural defect in the neural arch situated at the pars interarticularis. In Harris's[2] series of 100 cases the fifth lumbar vertebra was affected in 92 and the fourth lumbar vertebra in 8. Anomalous ossification of the three primary centres has been advanced as the reason for the presence of fibrous tissue at this site instead of bone, but there is no evidence to support this view. Hitchcock,[3] after examining 90 foetuses, concluded that the isthmic zone (the narrow part of the neural arch) is one of great potential weakness, since it consists largely of cartilage until after birth. Severe hyperextension of the spine, as might occur during a breech delivery, can cause the inferior articular facets of the fourth lumbar vertebra to impinge upon the pars interarticularis of the fifth with sufficient force to disrupt the neural arch at this point.

There are two types of defect: prespondylolisthesis or spondylolysis—here there is no forward slipping or displacement of the vertebra concerned—and spondylolisthesis, where the defect is accompanied by a forward slip of the vertebral body of varying degree, leaving the neural arch and inferior articular process behind. The displacement may be so great that the fifth lumbar vertebra lies in front of the first sacral body. In pseudospondylolisthesis, which occurs most commonly in middle-aged and elderly women at the level of the fourth and fifth lumbar vertebrae, there is no break in the pars interarticularis. This can easily be demon-

[1] *J. Amer. med. Ass.*, 1954, **154**, 398.
[2] *Ann. Roy. Coll. Surg. Engl.*, 1951, **8**, 259
[3] *J. Bone Jt Surg.*, 1940, **22**, 6.

strated by measuring the distance between the tip of the spinous process and the anterior border of the vertebral body: if there is no gap in the pars this measurement is the same as that of the vertebrae above and below the affected vertebra.

In 55% of Harris's cases of spondylolisthesis the onset of symptoms dated from an injury. The commonest complaint by the patient is of low back pain of gradual or sudden onset. Pain may also be present along the course of the fifth lumbar or first sacral nerve due to pressure on the root from an extruded nucleus or annulus or from an irregular intervertebral foramen. Occasionally the condition is painless. Diagnosis to a large extent depends on accurate and clear radiographs, the minor degrees of displacement being detectable in oblique views. When more than 30% of the vertebral body has slipped forwards the fifth lumbar spine is prominent, there is an increased lumbar lordosis, flank creases are present, and the trunk may appear to be shortened.

Colonna found that over four-fifths of his patients required only conservative treatment for the relief of their symptoms, and this is in accord with the views of British orthopaedic surgeons. Operative treatment need seldom be considered in patients over the age of 30. Exercises to strengthen the erector spinae muscles are helpful, whether or not a surgical corset is worn. Reduction of the displacement by skeletal traction is not usually advisable. Operative treatment, when it is considered necessary, aims to produce stability by lumbosacral fusion: this may have to be preceded by decompression when there is evidence of root pressure. Posterior fusion presents technical difficulties, and a few surgeons advocate anterior transperitoneal fusion, but this can be a hazardous procedure—for instance, when the inferior vena cava bifurcates at a lower level than usual. Gill, of San Francisco, has recently reported success by limiting the operation to removal of the loose lamina and the fibrocartilaginous tissue at the site of the defect, on the basis that the symptoms are due to nerve root compression and irritation rather than instability.

EXPLOSIONS OF BOWEL GAS

The explosion risks from inflammable anaesthetic vapours and static electricity have long been recognized. Another type of explosion risk, from ignition of gases in the colon, is certainly rarer and less well known.[1] Few surgeons who use diathermy in the rectum have had the misfortune to experience an explosion of bowel gases, but those few who have will realize how serious can be the consequences of this procedure. A number of cases have been reported in which an intraluminal explosion resulted in extensive rupture or massive ecchymosis of the colon above the treatment site. In one case[2] two adenomata were being treated with high-frequency diathermy, when there was a violent explosion and a blue flame shot out of the end of the sigmoidoscope. At laparotomy shortly afterwards a number of lacerations were found in the upper part of the descending colon which necessitated an extensive resection.

The intestinal gases are variable in both quantity and composition, being derived partly from swallowed air, partly from the diet, and partly from the blood stream. Nitrogen is usually the chief constituent of the rectal gases, but hydrogen and methane predominate in patients on leguminous and milky diets. Carbon dioxide is said to constitute about 10% of the rectal gas and oxygen less than 1%, so it might be thought that the oxygen necessary to support combustion could come only from the atmosphere via the shaft of the endoscope. Once air is admitted to the bowel at operation all the elements of an explosion are present—inflammable gases, a closed space, and an electric spark. The latter may be derived not only from the diathermy machine but also from defective insulation on the lighting system.

That oxygen in the lower bowel does not only get there via the anus is apparent from the evidence of Maddock *et al.*[3] These workers showed that swallowed air (and much air swallowing sometimes occurs during induction of anaesthesia) could reach the anus in half an hour. With certain anaesthetic techniques peristalsis is enhanced and air may reach the rectum even quicker; and if oxygen is given under pressure without a cuffed endotracheal tube it may be forced into the stomach.[4]

The risk of explosions in the alimentary tract is not confined to the large bowel. Galley[5] has recently referred to several interesting cases in which stomach gases eructated by sufferers from pyloric stenosis were ignited during the lighting of cigarettes. Quite recently in this *Journal*[6] we reported a case in which no explosive anaesthetic agent was used and yet the stomach was disrupted by an explosion as the face mask was removed. A discharge of static electricity from the anaesthetic mask may well have been the source of ignition in this case.

To guard against the risk of explosions in the colon some operators try to pack off the bowel with gauze above the treatment site. But this will not guarantee full protection, since gas may leak back past the pack and then be ignited. There are, in fact, a number of published cases in which explosions have occurred despite this precaution. The simplest way to maintain non-explosive conditions in the bowel during diathermy is by working in the atmosphere afforded by some inert gas, such as carbon dioxide. It may be run into the bowel by means of a fine catheter inserted through the sigmoidoscope, and the gas is readily supplied by the anaesthetist from his apparatus. A further advantage of this method is that the stream of carbon dioxide displaces any explosive gases which may be produced by thermal decomposition of the tissues. Hydrogen is the chief gas produced in this fashion and it will be added to the other explosive gases already present in the bowel. Finally, it is essential to use high-quality diathermy apparatus with efficient earthing arrangements.

[1] Becker, G. L., *Surg. Gynec.*, 1953, **97**, 463.
[2] Carter, H. G., *Amer. J. Surg.*, 1952, **84**, 514.
[3] *Ann. Surg.*, 1949, **130**, 512.
[4] Burden, J. F., *British Medical Journal*, 1952, **1**, 972.
[5] *Brit. J. Anaesth.*, 1954, **26**, 189.
[6] *British Medical Journal*, 1952, **1**, 168.

STRAIGHT AND CROOKED THINKING IN MEDICINE*

BY

RICHARD ASHER, M.D., F.R.C.P.

Physician, the Central Middlesex Hospital

As doctors we like to be men of action as well as thinking men, but, however much we act, every action is preceded by a certain amount of thought—or ought to be. It is worth paying attention to the way we are thinking, studying whether our reasoning is sound or unsound, whether we have any faults of thinking, whether we are unconsciously using methods of thinking which are illogical or even irrational, and seeing if we can improve the quality and effectiveness of our thought.

Thouless in his valuable book, *Straight and Crooked Thinking*, classifies thirty-four dishonest tricks of argument (and very ingenious they are too), but his work is largely devoted to political thought—a field in which the quantity and variety of crooked thinking are of quite a different order from those of medicine. In considering medical crooked thinking, I have purposely not used much systematic classification, because one form of crooked thinking common in medicine is caused by over-classification and the forcing of facts into the compartments provided for them, whether they fit or not. I am therefore considering straight and crooked thinking in medicine under the headings of therapeutics, statistics, causes, words, etc., but without formal classification.

Most medical thinking is based roughly on formal logic, a subject which is rarely studied to-day, though it is used unconsciously in much of our reasoning. Logic teaches a man to recognize what conclusion can be drawn from a series of statements (called premisses), and if logic is correctly applied to true statements it must infallibly follow that the conclusion drawn from them is correct. For instance, if we consider the two premisses (1) all cats are mammals, and (2) all mammals have hair, then it follows inevitably that all cats have hair. Those of you who have learnt formal logic will recognize this as a syllogism in the mood of Barbara. Similarly, if we take the statements (1) all cats are quadrupeds, and (2) all dogs are quadrupeds, it does not follow that all cats are dogs, because there is what logicians call an undistributed middle term—the term quadruped is not distributed entirely to dogs—only some quadrupeds are dogs, not all of them. The use of logic can be extended to cover a much larger number of premisses. Here is an example with three premisses from a book on logic: (1) no one takes in *The Times* unless he is well educated; (2) no hedgehog can read; and (3) those who cannot read are not well educated. From this it follows conclusively that no hedgehog takes in *The Times*.†

Therapeutics

In medicine most of our premisses are the facts found by research workers, and many of the conclusions from these facts become translated ultimately into ideas about the cause and treatment of disease. Research proceeds now at so great a rate that it is essential that reasoning must keep pace with fact-finding. As much trouble must be taken in reasoning from facts as it is in establishing their truth. Though medical data may not always be subjectable to the rigid application of formal logic, most views on therapy have behind them some attempt at a logical argument. The premisses and the arguments are not always expressed openly, so that crooked thinking is often concealed behind an impressive and persuasive array of words (particularly in brochures accompanying proprietary remedies). It is a profitable and useful exercise for all those who wish to think straight to analyse reasoning and weigh evidence by exposing the bare bones of an argument, and see how it looks. Do we not sometimes find that we are being influenced by arguments of this kind: (1) small people do not grow enough, (2) anterior pituitary makes rats grow, (3) therefore small people need anterior pituitary; of this sort: (1) pregnant rats without vitamin E miscarry, (2) therefore women who miscarry need vitamin E?

Let us consider some of the premisses again. (1) Anterior pituitary makes rats grow. Can we deduce anything from this? Can we even say because anterior pituitary makes rats grow that undue smallness in rats is due to lack of pituitary. Not necessarily, although it sounds quite reasonable. We are really saying if A causes B, then lack of A causes lack of B. Let us try this argument on something else. By the same process of reasoning we can argue living at a great height causes polycythaemia, therefore anaemia is caused by living at a great depth. Can we even argue that, because rats deprived of vitamin E miscarry, giving vitamin E to rats will prevent them miscarrying? If lack of A causes B, will plenty of A prevent B? Again a little thought will show how fallacious this argument is—for instance, lack of water causes rats to die, but giving them plenty of water will not make them immortal.

I am not arguing from this that pituitary extracts have no place in the treatment of dwarfism, nor vitamin E in the prevention of abortion, but I do say that a very different set of premisses and deductions are needed to give a logical basis to their use.

The logical approach to therapeutics is first to make a hypothesis from available facts from which we can deduce that some substance might benefit a condition, and then proceed to a controlled clinical trial to find whether it really does do so.

In other words, when we consider a line of treatment we start with the question "Should it work?" and finish with the question "Does it work?" Too many treatments are still advocated merely because there is a theoretical reason why they should work and without a practical controlled test being done to see whether they do work. For instance, because creatine excretion is increased in muscular dystrophy and glycine by mouth increases the supply of creatine to the body, the administration of glycine to sufferers from muscular dystrophy was advocated for a good many years without any convincing evidence that it was effective.

Are we not prone to accept a drug as effective in treatment because it ought to work rather than because it does work? Undoubtedly we are. Is there not a tendency to be convinced that because a drug reduces gastric acidity it does heal gastric ulcers, that because a drug increases cardiac output it benefits cases of heart failure, or that because a drug kills micro-organisms in a Petri dish it will kill them just as well in a living patient? The theoretical and laboratory tests for the effects of treatment are an essential part of clinical research and are responsible for many brilliant advances in therapeutics, and doctors must be on guard against being converted too readily to a line of treatment by theoretical arguments until these are supported by practical clinical tests.

Clinical Trials

When we are organizing practical clinical tests is it not crooked thinking to assess the success of treatment by measurements of associated factors not intimately related to the disability? Splenectomy, for instance, may be highly

*Chairman's address to the Middlesex County Medical Society, on September 24, 1953.

†This example is quoted from Lewis Carroll's *Symbolic Logic*, which is recommended as a diverting book providing stimulating exercise in logical thinking as well as a refreshing allowance of Carrollean humour.

beneficial in cases of congenital haemolytic anaemia, yet measurement of the fragility of the cells after splenectomy would show no improvement. Phenylbutazone may relieve a man's rheumatism enormously without necessarily bringing down his sedimentation rate.

There is no illness in which clinical improvement has been so variously assessed as in rheumatoid arthritis. As well as sedimentation rates we have instruments to measure the angular range of movements, graduated metal rings to measure the circumference of joints, dynamometers to measure the strength of grip, eosinophil counts to see what cortisone is doing to the blood, and yet anyone who has worked for long with rheumatism finds all these tests of little value compared with the direct measurement of the disability. Here in the cortisone clinic we may record weekly the time a patient takes to button up her stays or to lace up her shoes. We see how long she takes to walk the length of the ward, and note whether she can brush her hair or peel her potatoes.

Perhaps to younger people these tests seem less scientific because of their homeliness, but there is really nothing unscientific about them. Helmholtz said that all science is measurement, and many of these homely data can be measured quite informatively—the volume of soup spilled by a patient with tremor can be measured, the time to do up buttons can be charted, the amount of potatoes peeled in a standard time can be weighed, and so on.

Another error of thinking which profoundly influences therapeutics is to believe that improvement after treatment is due to treatment, the *post hoc ergo propter hoc* argument. Stated as bluntly as that, it seems obviously invalid, but hundreds of remedies are advocated on little better argument. In truth, the reasons a man may feel better after a pill are numerous—he might have felt better anyway, he might have felt better because he had such faith in the pill, he might have felt better because you had such faith in the pill, or he might really be improved by the pharmacological action of the pill. The best evidence of the effectiveness of a remedy is to have randomly allocated groups of patients —one treated with the substance, one with its inert counterpart—and nobody (doctor, nurse, or patient) having any idea which is the treated and which the untreated group. Now, the nature of treatments and the numbers of patients with particular illnesses make such ideally controlled experiments not always possible, but there are many treatments in common use to-day which have never been subjected to such testing—many drugs whose efficacy has never been scientifically demonstrated.

Use of Vitamins

If I had to suggest one particular field of therapy which needs to come under the scrutiny of statistical clinical trial it is the use of vitamins. More than two million pounds' worth of vitamins are prescribed each year under the National Health Service, and evidence that they do much good is very scanty. Are we not accepting arguments of this kind: (1) people deprived of vitamin B have sore tongues, (2) therefore everyone with a sore tongue needs extra vitamin B; (1) people deprived of vitamin C heal their wounds slowly, (2) therefore everyone with a wound needs vitamin C. These arguments alone are not rational—for instance, people deprived of salt for long enough may become mentally confused, but not everyone who becomes mentally confused needs salt.

The laity, too, have got the idea that as vitamins are essential to life any food that is full of vitamins is extra good for them. Subconsciously, I think they have adopted a sort of mathematical crooked argument that A is good, therefore 2A is twice as good and infinity × A is infinitely good. This is a dangerous argument. Cobalt, for instance, is (in minute quantities) essential to life, so is sulphur, yet a diet saturated with these substances might prove fatal. An even more dangerous use of the argument that 2A must be twice as good as A is, if one person has a moderate supply of wisdom and administrative ability, that ten people (that is to say, a committee) will function with ten times that wisdom and administrative ability. Those of you who have tested this hypothesis in practice know how sadly untrue it is.

But to return to vitamins—the reason why they provide such a glorious field for the polytherapist and the commercial chemist is that they are more or less harmless (apart from very heavy doses of vitamin D). Therefore any doctor can prescribe them with the argument, "If you have vitamin deficiency, they will do you good; if you haven't vitamin deficiency, they can't do you harm—therefore logically we might as well prescribe them for everyone." This argument is dangerous for these reasons: (1) by extending the argument we would find ourselves giving every member of the population an enormous number of vitamins and drugs; (2) if people are given vitamins they receive an impression that their diet is defective; (3) the cost to the country is enormous; and (4) people receiving a form of treatment (even if it is prophylactic) are more liable to believe they are unhealthy.

In our attitude to preventive medicine we have got to be careful that too much of the "can't do harm might do good" argument does not lead to an excess of prevention. We must not be so busy preventing disease that we have no time to enjoy freedom from it.

I read once in an American health pamphlet that every father returning from his day's work should remove his coat and wash his hands in disinfectant before touching any of his children. Perhaps there may be a logical case from the hygienist's point of view, but if that went too far we might finally reach this sort of situation: "Oh, father, lift me up; there's a band marching past the window." "Certainly, my boy; just wait while I gargle and put on my mask and rubber gloves."

But I must return to my theme, which is that in therapeutics there must be good evidence from controlled statistical trials that what is being given is doing good. Here I should like to issue a warning that the mere use of statistics is no guard against crooked thinking. The danger of crooked statistics is that its fallacies are less likely to be noticed because of the mixture of awe, suspicion, and reverence with which statistical thinking is regarded by most of us.

An Example

Here is an excellent example of statistical crooked thinking. An investigator published an article showing that of 200 epileptic subjects, 24% had had infantile convulsions in the first two years of life, whereas of 200 normal subjects only 2% had had infantile convulsions. He went on to argue that the pronounced difference between the 24% in the epileptics and in the 2% in the control group made it clear that convulsions within the first two years of life ought to be taken as a manifestation of epilepsy and that any child having convulsions in infancy should be treated with anti-convulsant drugs for several years. The argument appears most convincing, doesn't it? The fallacy is not at all obvious. The incidence of epilepsy in the population has been left out. Now, this is about 1 in 400. So among 40,000 people there would be 100 epileptics, 24 of whom had infantile convulsions. But among 40,000 people there would be 800 normal people (2% of 40,000) who had suffered from infantile convulsions. So it would mean treating 800 people, of whom only 24 had epilepsy—in other words, submitting 32 normal children to prolonged anti-convulsant therapy in order to make sure of treating one epileptic early in life. I mention that article in detail to show the danger of being swayed by impressive figures.

Causes

Another perversion of thought applicable to statistics is to believe that a statistical relationship between two things implies a causal relationship between them. It does not do so. It is very probable that statistics would show erythroblastosis foetalis to be twenty times less common among

the offspring of opium smokers. This is no argument for encouraging opium smoking in the maternity wards. It depends on the fact that opium is largely a Chinese habit and that 99% of Chinese are rhesus-positive, and so cannot produce erythroblastosis foetalis. Similarly, if rheumatic fever is significantly more common in those who have sucked dummy teats in childhood, it may only mean that rheumatic fever is commoner among the poor, and so is dummy-sucking. If A varies with B, it does not show that A causes B.

Logic and the Laboratory

I now ask you to consider an attempt at rational thinking applied to the use of laboratory investigations. As regards tests of function, are we not inclined to argue, (1) this test measures the conjugation of benzoic acid; (2) the conjugation of benzoic acid is a function of the liver; (3) therefore this test measures the function of the liver? Might we not equally well argue, (1) this factory produces smoke; (2) this test measures the amount of smoke produced; (3) therefore this test measures the productivity of a factory? The point is that livers and factories both do a number of things, and measuring one of these things does not measure all of them.

Also it is in the ordering of laboratory or radiological investigations that rational thinking is so necessary. It is a salutary exercise in mental discipline to catechize oneself when ordering any medical investigation, saying, "Why do I order this test? What am I going to look for in the result? If I find it will it affect my diagnosis? How will this affect my management of the case? Will this ultimately benefit the patient?"

It would be only rarely that we could answer all these questions satisfactorily, as, for instance, in ordering a Wassermann test and a Lange curve on the cerebrospinal fluid of a patient suspected of dementia paralytica. Perhaps it would be a good idea to have a space on every laboratory form in which the doctor had to state exactly why he had ordered a test. I believe if answers were honestly filled in we might get this sort of thing:

(1) I order this test because if it agrees with my opinion I will believe it, and if it does not I shall disbelieve it.

(2) I do not understand this test and am uncertain of the normal figure, but it is the fashion to order it.

(3) When my chief asks if you have done this or that test I like to say yes, so I order as many tests as I can to avoid being caught out.

(4) I have no clear idea what I am looking for, but in ordering this test I feel in a vague way (like Mr. Micawber) that something might turn up.

(5) I order this test because I want to convince the patient there is nothing wrong, and I don't think he will believe me without a test.

Words

Finally, I want to consider the effect of words on thinking. Words not only provide a vehicle for conveying thought, but even provide wings for its flight which make it travel either straight or crooked.

One trouble with words is that if there is a word for a particular thing we become convinced that such a thing exists: this trouble makes precise work so difficult, particularly in the field of psychiatry.

If there is doubt whether, say, a patient is suffering from mania or catatonic schizophrenia, the observer is inclined to think there must be an answer—he believes these two diseases exist as nosological entities. Yet, as there are no truly objective tests to settle the matter, it might be wiser to regard such terms as descriptions of behaviour with no more privilege to exist as diseases in their own right than have conditions such as restlessness, talkativeness, elation, and the like.

It is often helpful to straight thinking to pause and consider what we are meaning by a word, for we may find it is playing tricks on us. Take the word "typical," for instance. If we hear in a chest those musical rales that may occur in a pneumothorax and we describe them to students as typical, we may convey to the student they are common, whereas we really mean they are classical (always mentioned in books) or diagnostic (making the diagnosis certain).

A similar self-catechism is helpful if we use words like natural, unnatural, normal, or abnormal, or the word "purpose," and if we ask ourselves exactly what we mean by them we may realize how uncertain we are what we are thinking.

Another source of crooked thinking caused by words arises from the bestowal of a name indicating a pathological process when describing only a symptom or syndrome. We call the common cervico-dorsal myalgia of our out-patients "fibrositis," but we have no notion whether it is caused by inflammation of fibrous tissue or not. We call the symptoms following gastrectomy "the dumping syndrome," though there is still no general agreement regarding their cause. Socrates said, "He who first gave names, gave them according to his conception of the things which they signified, and if his conception was erroneous, shall we not be deceived by him?"

One word which encourages crooked thinking is becoming increasingly popular at the moment—the word "group." We say this probably belongs to the allergic group, the psychosomatic group, or the collagen group, without having any very clear idea of the boundaries or contents of those groups. We use them to cloak our ignorance, feeling that once we have cast diseases into these vast receptacles, these aetiological dustbins, they are satisfactorily accounted for. I believe that those brave enough to lift the lids off these bins and poke about among the rubbish there may find clinical salvage of inestimable value.

Another word is to be deplored because it allows woolly thinking to flourish. This is the word "imbalance." The word could be expunged from the medical vocabulary without any loss. Whenever we read of autonomic imbalance or endocrine imbalance we are in for a piece of nebulous thinking. It is all right to suggest a disease is associated with overaction of the sympathetic or underaction of the parasympathetic, or due to too much suprarenal cortical secretion or too little thyroid secretion, but to leave it imprecisely labelled as due to imbalance is a travesty of thinking that should not have survived the discipline of a scientific education.

Conclusion

I must apologize for the rather vague way I have wandered from one subject to another. All I have tried to suggest is that we ought to be increasingly critical of our own and other people's thinking, to analyse all arguments that our books, our teachers, and ourselves are using; to seek out crooked thinking and avoid it, and to follow the path of straight thinking, wherever it may lead us, guided by those helpers of whom Kipling wrote:

> I keep six honest serving men,
> They taught me all I knew;
> Their names are what, and why, and when,
> And how, and where and who.

A medical mission comprising two doctors, two technical health assistants, and two male nurses accompanied the 3,173 pilgrims who went to Mecca in 1953. It was provided with an adequate and varied stock of medicaments, surgical equipment, and a large refrigerator. More than 6,000 consultations were given (skin diseases 29%, digestive troubles 10%, surgical cases 5%, malaria 3%, miscellaneous 53%). The general state of health is reported to have been excellent. No case of infectious or epidemic disease was notified either during the voyage or after the return of the pilgrims. There were 32 deaths (1% as against 2% in 1952) due to sunstroke, diseases of the circulatory system, and debility in aged persons.—W.H.O. *Weekly Epidemiological Record*, No. 31, 1954.

Nova et Vetera

D. C. DANIELSSEN, ZOOLOGIST AND LEPROLOGIST (1815–94)

In the summer of 1954 the Norwegian wireless sponsored a series of lectures on Norwegian pioneers of medicine with an international reputation. The lecture on Danielssen was delivered by Dr. Tschudi Madsen, who traced the career of the son of a watchmaker in Bergen, destined a century ago to become the leading world authority on leprosy. Danielssen was apprenticed in his thirteenth year to an apothecary, from whom he had to part barely four years later on account of tuberculosis of the hip, which confined him to bed for more than a year. This diversion led to his study of medicine, three years of which made him an "Examinatus Medicinae" in 1838. A year later he returned to his native town, where he devoted himself to an intensive study of leprosy, which was spreading at an alarming rate. The first census of lepers, undertaken in 1836 by the clergy, had revealed only 650 cases. By 1845 this number had risen to 1,125, and by 1856 to "at least" 2,858. In coping with this new wave of leprosy, the authorities provided hospitals, which, in the case of Bergen, evoked protests from the public. One of its spokesmen prophesied how unfortunate would be the reaction of pregnant women exposed to the sight of lepers allowed to enjoy the liberty of the streets.

In co-operation with Wilhelm Boeck, professor of dermatology at the University of Christiania (now Oslo), Danielssen published a monumental study which quickly established his international reputation as a leprologist. He was placed in charge of the leper hospital in Bergen. Because of his repeated failure to inoculate others, himself included, with leprous lesions, he believed that leprosy must be hereditary. It may be noted in passing that Danielssen's successor, Armauer Hansen, the discoverer of the bacillus of leprosy, was dismissed from his appointment as head of the leper hospital because he had attempted to inoculate a woman leper with material from another leper. Arguing in terms of heredity, Danielssen pleaded in vain for the compulsory segregation of lepers with a view to the prevention of breeding of leprous stock. It was Hansen's demonstration of the bacillus of leprosy that induced the authorities ultimately to consent to segregation.

Danielssen's contribution to zoology was probably his greatest work. Even before he became a medical student he took part in a botanical expedition in the interior of Norway, and for the rest of his long life he made the Bergen Museum his headquarters. He found it as a modest private collection of specimens, and he converted it into one of the most important biological museums in the whole of Europe. Only a couple of hours before his death in 1894 due to severe anaemia, he was engaged on a lively discussion of a case of actinomycosis, the first to be observed on the west coast of Norway.

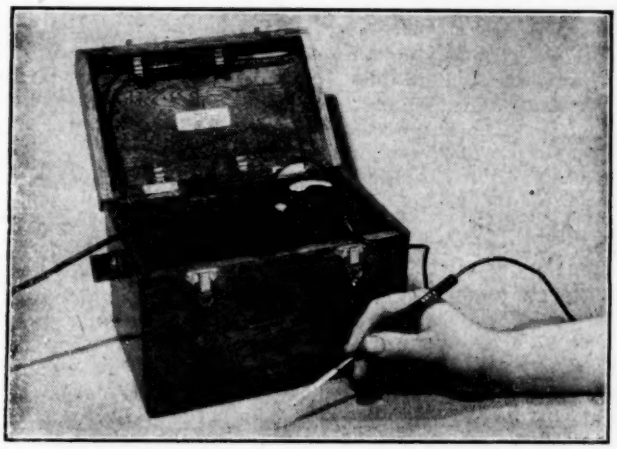
A bust of Danielssen in the vestibule of the Bergen Museum shows him as a striking old man with a flowing beard. Frail of build and with a limp due to his old tuberculosis, Danielssen more than compensated for these physical handicaps by the natural dignity with which he met the world. All his four children died of tuberculosis, but it was never to crush him. With his happy gift for coaxing funds and willing co-operation out of State and municipal authorities, he successfully represented Bergen for many years at the Storting in Christiania. An excellent host, he was something of an epicure, a quality reflected in his wine-cellar. It was bequeathed to two of his colleagues, one of them the leading teetotaller in Bergen. He left his fortune to the Bergen Museum, and his collection of paintings to the Bergen Art Gallery. Visitors to Bergen will find a painting of Danielssen in the Haukeland Hospital.

CLAUDE LILLINGSTON.

Preparations and Appliances

HEAVY DUTY SURGICAL CAUTERY

Dr. WALTER CALVERT, consultant obstetrician and gynaecologist, Stockport and Buxton Hospitals Group, writes: The equipment illustrated below was designed for cauterizing the cervix, but has been found suitable for certain general surgical procedures also. It is designed to obviate disadvantages of other instruments. The hot-wire loop type of instrument, for instance, is unsatisfactory for gynaecological purposes. Its temperature is too high and its total heat content is too low, so that it tends to cut a small portion of tissue rather than to burn or coagulate a larger area superficially. Again, the small mass of hot wire is quickly quenched. Another type of instrument available overcomes these disadvantages but has others. The heating element is external to the blade and is so thick that there is danger of accidental burning of the vulva or vagina. The mounting of the heating element is fragile. Moreover, the instrument is not made in this country. Surgical diathermy is not satisfactory for the treatment of cervical erosions, though



widely used. It is unsuitable in the post-natal clinic, where the instrument described here has been found particularly useful. In the theatre, time is wasted while the diathermy pad is applied when an erosion requires treatment. There is also the danger of fire and accidental burning by incorrectly applied pads.

The new instrument is a modification of a miniature soldering-iron, made by Oryx Electrical Laboratories Ltd. for sub-miniature work on hearing-aids, etc., and my thanks are due to the principal of this firm, Mr. C. S. R. Wotton, for his personal and patient interest in producing exactly what was required. Greater modification was needed than was expected, mainly because of the surprising discovery that a considerably higher temperature is required for cauterizing human tissues than for commercial soldering.

The blade is of silver and the heating unit is inside it. In nearly two years of testing and use there has been no case of failure of the heating element. All parts are interchangeable. The cautery operates on any 12-volt supply, with a rheostat to control the temperature. A complete unit suitable for use on mains supply is available, so that the equipment is complete in itself. In designing this, emphasis has been placed on safety and reliability. There is no possibility of electrical shock either to patient or to operator.

The distributors are Messrs. Antex, 3, Tower Hill, London, E.C.3.

Correspondence

Detoxication of Drunkenness

SIR,—Since your publication of Dr. V. P. Wordsworth's letter (*Journal*, April 25, 1953, p. 935) on the sobering-up effect of vitamin B_6, this excellent remedy has been adopted here (100 mg. of "benadon" given intravenously). This scope of activity for B_6, we think, is limited rather to cases of excitation, and we have found the duration of this effect to subside in about one hour. Still, repeated injection of the remedy will again have the same effect.

Since August, 1953, we have been able with considerable advantage to make use of the investigations carried out by Stuhlfauth,[1] Berg,[2] Klein,[3 4] Pletscher,[5] and Pletscher together with Bernstein and Staub[6] with regard to the capacity of fructose to promote the metabolism of alcohol. We have found an increase in such metabolism amounting to 20 to 90%. We have found it even more significant, however, that the fructose-alcohol reaction has also a sobering-up and sedative effect on the patient, corresponding to the effect of vitamin B_6, but appearing more slowly, in about 30 minutes. On the other hand, the fructose effect persists somewhat longer, and is often followed by a desire for sleep, which, when satisfied, tends to leave the patient free from any desire for more alcohol. Thus, when B_6 and fructose are given at the same time, they are seen in their effect to supplement each other in a most beneficial way.

At first we used the pure fructose preparation "laevulose" from Deutsche Laevosan-Gesellschaft, Mannheim. But we have since arrived experimentally at an exceedingly simple procedure—using Danish honey. Indeed, it is a rather sweet mouthful the patient thus has to swallow, but as a rule he can readily be persuaded to take the dosage required per os. We have found the suitable dosage to be two doses of about 125 g. honey at an interval of half an hour. As is well known, half of the sugar content of honey is fructose. It should be mentioned that a larger amount of fructose given at once may produce a reaction with redness of the face, sensation of heat, palpitation, shortness of breath, nausea, and sometimes vomiting—that is, phenomena reminding one strongly of an antabuse-alcohol reaction. Like the latter, also, a severe honey-alcohol reaction may be counteracted by intravenous injection of antihistamine,[7] which reduces the cardiovascular phenomena and produces a feeling of relief.

Here it is also to be pointed out that the honey-alcohol reaction always subsides within half an hour (often it is quite transitory) and leaves no discomfort—in particular no feeling of that physical exhaustion encountered after an antabuse-alcohol reaction. In conclusion it is to be added that the fructose (honey) medication may very well be combined with the antabuse-antihistamine-sodium-chloride therapy.

We must admit that we are still unable to render a strongly intoxicated patient capable of work in a couple of hours. But, with the remedies mentioned here, at any rate, we have advanced so far that we will always be able to quieten him and render him "manageable." By means of antabuse-antihistamine administration we can always make him sleep within a couple of hours—largely by employing decomposition products of alcohol as hypnotic, leaving no drug sensation when the alcohol is all gone. In the absence of severe psychotic changes as the background for the alcoholism, a greater majority of intoxicated patients may thus be able to work already the next morning.—I am, etc.,

Copenhagen. OLUF MARTENSEN-LARSEN.

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4 Ibid., 1953, **44**, 1427.
5 *Helv. med. Acta*, 1953, **20**, 100.
6 *Helv. physiol. pharmacol. Acta*, 1952, **10**, 74.
7 Martensen-Larsen, Oluf (1953). *Quart. J. Stud. Alcohol*, **14**, 406.

Cortisone and Aspirin in Rheumatoid Arthritis

SIR,—Professor J. H. Kellgren's reply (*Journal*, July 17, p. 170) to our criticism (*Journal*, June 26, p. 1499) only succeeds in obscuring the essential point we wish to make—that there is a statistical fallacy in the Medical Research Council and Nuffield Foundation's report on a comparative trial of cortisone and aspirin in the treatment of rheumatoid arthritis, and that this is based on the fact that the cortisone-treated patients happened to begin the trial at a significantly higher level of function and so had less opportunity to show clinical improvement.

In its simplest terms the problem is this. A patient with a 15-degrees flexion deformity of the knee-joint regards the result of treatment producing full extension as perfect—100%. A patient with a 45-degrees flexion deformity does not regard 15 degrees improvement as perfect; the effect is not 100%. What is it? This is the problem; and it is not solved by expressing changes either as percentages of the initial values or in absolute values, as Professor Kellgren appears to think. If we could determine the level of function attainable if the total amount of reversible disability were removed, this would constitute the ideal yardstick, but we cannot do so. All we suggest is that to express improvement as a percentage of the improvement possible up to an average normal is less erroneous than the method employed by the committee. The initial values of the cortisone and aspirin groups were not comparable, and this difficulty was not taken into account. Had the experiment been planned differently, this difficulty could have been avoided. Now it has occurred, it must be faced or evasion leads to an invalid conclusion.—We are, etc.,

GEOFFREY E. LOXTON.
London, S.E.18. DAVID LE VAY.

Intramuscular Iron

SIR,—I feel that the letter of Dr. David Thomas (*Journal*, July 31, p. 303) calls for some comment. Anyone who has used intravenous iron therapy extensively and has seen the painful reaction that can occur due to accidental extravenous injection would, I am sure, hesitate to give deliberately into the tissues any of the saccharated iron oxides at present on the market. In the case that Dr. Thomas mentions there is no evidence that the "ferrivenin" was actually utilized. His patient was already on oral iron, and the fact that there was no rise in the haemoglobin after three days is no indication that oral therapy was going to be ineffective. The dose of intramuscular iron given (2.5 ml. "ferrivenin" twice weekly in less than three weeks) was presumably only 300 mg. Calculated by the usual formula—4% rise in haemoglobin per 100 mg. iron injected—this amount of iron would raise the haemoglobin level by approximately 12%, whereas the patient's haemoglobin rose 36%. Doubtless the oral iron given at the same time played an important part in this response.

Nevertheless Dr. Thomas has mentioned a topic of considerable current interest—namely, intramuscular iron therapy. As was intimated in these columns recently by Drs. F. Fletcher and E. London (*Journal*, April 24, p. 984) a new preparation of iron suitable for intramuscular injection had been undergoing extensive clinical trials at various centres. At Saint Mary's Hospitals we have now treated more than 120 patients with this preparation. As much as 250 mg. daily for seven days has been given to some patients without any serious general or local reactions and with very satisfactory therapeutic results. The results of these trials will be published in the near future.—I am, etc.,

Manchester, 13. R. F. JENNISON.

SIR,—Dr. David Thomas's letter (*Journal*, July 31, p. 303) prompts me to record the following. A very anaemic 44-year-old female attended a busy morning surgery here and was given a supply of "ferrivenin" with instructions to go home and await the arrival of one of us to commence treatment. In her enthusiasm to begin therapy she called on the district nurse, who promptly gave her 5 ml. into the left

lower buttock. On returning to the same operator that evening with a complaint of some local discomfort little sympathy was shown and a further 5 ml. were injected in precisely the same spot. I saw the patient daily for the ensuing 10 days, and, apart from a moderate degree of local reddening and swelling, no real ill effects followed.

It would appear that the ill local effects of "ferrivenin" given extravenously have either in the past been grossly exaggerated or there is a considerable variation in the reactions of different patients.—I am, etc.,

Beauly. J. G. MUNRO.

Threescore Years and Ten

SIR,—The National Council of Social Service has recently produced a report with the title of "Over Seventy," in which they give still further light on the care of the aged. When this report came to my notice by way of a review in the daily press, I suddenly realized what a vast amount of my time in the last quarter of a century or so had been consumed by this problem of the care of the aged. I could not, however, find any ready means of estimating what proportion of my work was given up to the "over seventies," but I did discover that for most of this period I had (for some reason quite unknown) retained the counterfoils of all the death certificates issued by me from 1929–53 (except for two years, 1944–6, during which time I was in the Services). I have therefore extracted the following tables of figures from them, in which it will be seen that, excluding babies under 1 year of age, the average age of the remainder was about 74, and that about three-fifths of the total were between 70–90 years of age.

TABLE I

Year	Male	Female	Total	Average Age	Deaths Under 1
1929	14	6	20	62	2
1930	15	14	29	68	1
1931	10	13	23	73	0
1932	13	11	24	72	2
1933	11	14	25	61	0
1934	10	6	16	65	1
1935	11	14	25	77	1
1936	15	6	21	73	1
1937	11	3	14	70	1
1938	9	12	21	73	2
1939	13	12	25	71	0
1940	15	17	32	71	1
1941	10	23	33	73	3
1942	16	15	31	74	1
1943	15	12	27	69	3
1944–6	12	14	26	71	1
1947	9	11	20	76	1
1948	13	9	22	72	0
1949	14	10	24	77	1
1950	15	11	26	72	0
1951	17	17	34	73	0
1952	14	15	29	72	1
1953	17	9	26	72	0
	299	274	573	74	23

TABLE II

Age Group	Male	Female	Total
Under 1 year ..	12	11	23
1–9	3	2	5
10–19	1	0	1
20–29	0	4	4
30–39	2	5	7
40–49	8	10	18
50–59	28	19	47
60–69	59	50	109
70–79	108	86	194
80–89	67	78	145
Over 90	11	9	20

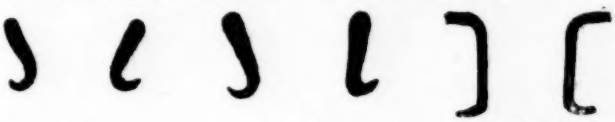
A further examination of the certified causes of death in these 573 cases show that the four main conditions were: senile myocardial failure or other cardiac lesions (180), cancer (90), cerebral thrombosis (73), and cerebral haemorrhage (57), which account for 400 out of the 573. It must be agreed that most of the deaths in the younger age groups occur in hospital or become the business of the coroner as the result of accident, so that the G.P. is left with this hard core of chronic sick and infirm. This point is one which cannot be stressed too much to the new entrants into general practice. In this list of 573 deaths there were no rare diseases, but many long-standing conditions such as chronic pulmonary tuberculosis, chronic nephritis, and chronic bronchitis and asthma. In the early years of this series there was no help from the sulphonamides and antibiotics, so that there appear the odd deaths from measles and septicaemia, quinsy and whooping-cough, and such-like. This death rate at the average age of 74 represents much chronic sickness, as most of them are in indifferent health for years before they finally depart this life.

Any practitioner will know how exacting this work can be if it is done properly, as every one of these old folk is an individual with a multitude of symptoms, the majority of which have never seen the light of day in textbooks. It is felt that the main object in the treatment of all these conditions associated with age should be directed towards the patient's comfort, irrespective of the scientific approach to their disease. They should never be put on to diets, etc., but the practitioner should be guided by the axiom of "a little of what you fancy does you good." Drastic and painful courses of treatment are not warranted when the best they can achieve is the extension of life for a further month or so. Specialists in geriatrics are the worst offenders in this line of treatment, it is found. Finally, the main object should be to create confidence and a contented mind in these old people and to relieve any pain and suffering by whatever means you can, however unscientific the treatment may be.—I am, etc.,

Ringwood. REGINALD H. LITTLE.

Mastoid Retractors

SIR,—Two years ago you kindly published for me the description of "An Irrigator for the Fenestration Operation" (*Journal*, August 23, 1952, p. 441). In that description I omitted to mention that the irrigator was originally designed for use with Graham's mastoid retractor. Although the irrigator can be used with other retractors, Graham's is the most convenient. In this instrument the blades are parallel, so that when the "guide tubes" are in place they lie vertical to the skin surface. With other types of retractor, in which the blades converge, the "guide tubes" also converge, making adjustment of the polythene tubing difficult. This difference is demonstrated by the diagrams, which show the end views of Graham's and two other retractors.



The mastoid retractors in common use were designed for the post-aural approach to the temporal bone. Graham was, I believe, the first in this country to design one for the end-aural approach; the original was made in 1933. It is a very good retractor and has been in regular use at St. Mary's Hospital for many years. The parallel blades give better deep retraction than do converging ones, and their size and shape are excellent. The retractor is opened by a powerful rack and pinion.

The instrument can be obtained from Willen Brothers, of New Cavendish Street, London, W.1.—I am, etc.

London, W.1. P. H. HUGGILL.

Haematological Indices

SIR,—In Dr. J. F. Wilkinson's compendious article on "Laboratory Investigations in the Hyperchromic Anaemias" (*Journal*, June 12, p. 1370) it was understandable that much had to be omitted, but I think some further mention ought to be made of the relative usefulness of the haematological indices for the benefit of clinicians less familiar than Dr. Wilkinson with these. Dr. Wilkinson commented, with justification, on the inaccuracy of the colour index (C.I.), but he did not make it clear that the mean corpuscular haemoglobin

(M.C.H.) cannot be any more accurate, as it is dependent on the erythrocyte count in the same way as the C.I. In fact, a linear relation exists between the C.I. and the M.C.H.—that is, $M.C.H. = C.I. \times 29.6 \times 10^{-12}$ g., taking 100% haemoglobin ≡14.8 g./100 ml.

This dependence on the erythrocyte count is not, however, the only objection to the C.I. and the M.C.H. These indices are both complex functions of the mean corpuscular volume (M.C.V.) and the mean corpuscular haemoglobin concentration (M.C.H.C.). In other words, if we know the M.C.V. and the M.C.H.C., then neither the C.I. nor the M.C.H. adds any further information, because $M.C.H. = M.C.H.C. \times M.C.V. \times 10^{-2}$ $\gamma\gamma/\mu^3\%$. Thus any change in M.C.H. is attributable to a change in either M.C.H.C. or M.C.V. or both.

There is thus much to be said for discarding the M.C.H. altogether, and indeed for discarding also the semantically associated term "hyperchromic" in favour of "macrocytic."—I am, etc.,

Benghazi. F. O'NEIL YOUNG.

Sudden Death from Acute Pancreatic Necrosis

SIR,—The article on this subject by Dr. G. Williams (*Journal*, May 22, p. 1184) prompts me to record the sudden death of an infant of three months, where the post-mortem findings were typical of this disease. The patient, a healthy female Torres Strait Islander, was brought to the hospital at Thursday Island some years ago. The mother stated that the child had been fretful during the previous night, but was taking her feeds normally. An examination did not disclose anything of importance. The mother was instructed to take the child home and return on the following day. At about 10 a.m. next day the mother put the child down on a bed after giving it the usual feed. The child immediately gave a loud scream, collapsed, and died in a few seconds. Post-mortem findings disclosed extensive haemorrhagic pancreatitis with fat necrosis.—I am, etc.,

Duntroon, Australia. J. R. NIMMO.

Back to the Barber's Pole

SIR,—I should like to support Mr. A. K. Monro in all that he has said in his letter (*Journal*, July 31, p. 302). For the past fifteen years I have had the honour to work in collaboration with the consulting anaesthetist, who holds such a clinic, over the difficult and dangerous risks involved in certain major orthopaedic operations, particularly in very ill or fragile patients, referring them to him at the earliest possible opportunity for his opinion. In the case of the normal patient about to undergo a routine operation in nursing home or hospital, I always ask him to see the consulting anaesthetist on his admission.—I am, etc.,

London, W.1. B. WHITCHURCH HOWELL.

Rainbow Napkins

SIR,—We were recently baffled by a simple problem which may interest your readers. An intelligent mother of a 3-months-old bottle-fed baby complained that when the napkins contained a motion the stool was often surrounded by a salmon-pink discoloration which turned a deep bright mauve colour when hot water was poured on to the napkin. She was satisfied that this did not happen if the napkin was wet with urine alone; she was certain that nothing in the water or in the basin was responsible; and she stated that similar colour changes were sometimes noticed on the baby's clothes after a vomit.

The napkins she brought with her confirmed her description, and chemical tests revealed that the substance causing the colour change was phenolphthalein. The alkalinity of the napkins had caused the colour change when the phenolphthalein was washed out of the stool. Armed with this knowledge, the mother was seen again and on direct questioning admitted that she gave approximately one-third of a Steedman's powder twice weekly to the baby for constipation.

In spite of adverse publicity mothers still give babies teething powders, and, since the new formula for Steedman's contains phenolphthalein in place of calomel, it is likely that we shall be presented with these "rainbow napkins" quite frequently in the future. We hope that this simple explanation may be of use to others.—We are, etc.,

A. B. ANDERSON.
London, N.18. IAN G. WICKES.

Single Incision for Bilateral Orchidectomy

SIR,—In support of Sir Heneage Ogilvie's recommendation of the scrotal approach to the testis (*Journal*, June 5, p. 1324), I would like to point out that literally tens of thousands of operations for hydrocele, scrotal tumours, and operations for castration have been done and are being done through the scrotum in our hospitals in India and we have found this procedure fully satisfactory and safe.—I am, etc.,

Madras, India. B. RAMAMURTHI.

Visit to Poland

SIR,—As a graduate of the Cracow and Gdansk Medical Academies and a medical practitioner in Poland until April, 1953, I would like to comment on the views of Dr. Winifred M. Coppard after her 10-day visit to Poland (*Journal*, May 22, p. 1211) which I have only just seen.

It would be superfluous to deny that some progress has been achieved in the field of child care. As regards the provision of crèches, however, it must be emphasized that both their distribution and number leave much to be desired. In the city of Warsaw itself (population now over 900,000) the crèches can accommodate under 1,000 children, while in the housing estate of Nowa Huta (population approximately 45,000), situated near Cracow, there is only one crèche in operation, the remainder being unfit for use. According to the regulations in force each factory employing more than 500 women should provide a crèche. This regulation is not strictly observed. Frequent cases of infectious diseases and a widespread lack of confidence in the institutions provided by the Communist régime are sufficient to deter mothers from entrusting the care of their children to State-operated crèches or kindergartens; they only do so in cases of urgent need. It appears, however, that crèches are being more widely used, due largely to the pressure of economic circumstances. The gradual lowering of the standard of living of the masses and not the sight of war-time destruction, as Dr. Coppard suggests, is the main factor which compels Polish women to forgo the duties of motherhood.

The problem of tuberculosis assumes serious proportions in Poland and is no doubt related to general overwork, under-nourishment, and bad living conditions. In the urban centres 12 out of every 100 persons seeking specialist treatment are diagnosed as tuberculous cases. The problem is equally serious in the rural areas, where the incidence of zoogeneous tuberculosis is alarming. The tuberculosis mortality rate continues to be very high. Even according to official and, no doubt, tendentious sources, this rate is higher than that given by Dr. Coppard. (According to the statement made by the Polish Minister of Health on the occasion of the Public Health Congress in Warsaw in October, 1952, the tuberculosis mortality rate is 10.4 per 1,000. Dr. Coppard states that it is 8 per 1,000.) With regard to tuberculosis sanatoria, I would like to point out that side by side with the model establishments (such as the one Dr. Coppard was allowed to visit in the Tatra Mountains) there are scores of places where there are no facilities for chest surgery, no mobile ambulances, and where—as in a case which I myself saw—17 beds are put in a room with a floor space of about 140 square feet (12.6 m.²) and no provision made in the building for the most elementary sanitary facilities. It is a pity that Dr. Coppard made no attempt to question some of the patients in the model sanatorium she visited on what they had to go through before they were finally sent there. Even the Communist press in Poland makes no secret of how difficult it is to gain access to a

sanatorium. It is common knowledge in Poland to-day that, even after all the formalities have been completed, the patient who gets sent to a sanatorium may find on arrival that there is no vacant bed for him. According to the official Six-year Plan, the number of beds available for tuberculosis in all sanatoria will be 29,806 by 1955; Dr. Coppard, however, informs us that to-day there are already 108,000 beds available. Mass B.C.G. treatment for all children up to the age of 7 is undoubtedly a considerable achievement. I doubt, however, whether Dr. Coppard's figures are correct. According to the Ministry of Health in Warsaw, 3,100,000 children received B.C.G. in the course of the current campaign. I have reason to doubt whether as many as 4,900,000 children were born in Poland (population 25.5 millions) during the course of the past 18 months—a figure which Dr. Coppard's statement appears to demand.

A less prejudiced visitor to Poland might well have made the following general observations on the state of the health services: (1) The scope of the health service is not only inadequate but discriminatory. Besides the general health service there exist special services for a privileged group consisting of higher functionaries of the Communist party and members of the security police. Members of these bodies are entitled to the use of hospitals, sanatoria, and other facilities not accessible to the general public. The same kind of discrimination is to be found in the allocation of medicines and other medical supplies. (2) The degree to which a member of the public can gain access to some of the facilities provided by the State health service depends on the kind of work performed by the person concerned. Every person belongs to one of the four main socio-economic groups. Employees of State-operated enterprises are entitled to the use of all facilities provided by the State health services. All of these facilities, however, are completely denied to those who belong to the non-socialized sector of the economy—that is, peasants, craftsmen, and tradesmen. (3) Doctors (general practitioners and specialists) are compelled to work full-time in the State health service and must satisfy the norms laid down by the Government. Thus, a specialist in diseases of the lung must examine no fewer than five patients per hour. A general practitioner in the out-patients' department of a district hospital may not devote more than 18.2 minutes of his time to any one patient; this must include preliminary examination, *x*-ray treatment, the filling in of forms, etc.—I am, etc.,

London, W.2. WLADYSLAW TACREITER.

Smoking and Lung Cancer

SIR,—I do not understand why, when writing about smoking and lung cancer, some of your correspondents try to obscure the issue with unrelated verbiage. The evidence for a causal relation between smoking and lung cancer has been obtained by using methods logically identical with those which incriminated β-naphthylamine as a cause of bladder cancer—and I need hardly remind you that the manufacture of β-naphthylamine has ceased. Spontaneous bladder cancer is uncommon but not rare. Workers in certain chemical factories were found to develop bladder cancer more frequently and at a younger age than did the general population, and it was ultimately found that most of the workers with bladder cancer had been exposed to β-naphthylamine. At this stage restrictions were placed on the use of β-naphthylamine and animal experiments started. This is roughly the position to-day in the researches on the relation between smoking and lung cancer.

Doll and Bradford Hill in this country, and Evarts Graham in America, set out to discover whether smoking was related to lung cancer in the same way that exposure to β-naphthylamine is related to bladder cancer. Their task was complicated because exposure to smoking is common whereas exposure to β-naphthylamine is rare, and there were also suggestions that lung cancer might be commoner in towns than in the country. Both these and other possibilities were allowed for in the design of their experiments. The experimenters propounded the questions: "Is there any difference between the smoking habits of patients with lung cancer and those of patients with cancer at other sites; and if so, what is that difference?" The experiments were very simple; they selected two groups of patients, one with cancer of the lung, the other with cancer at other sites, and asked each patient whether he smoked or had smoked, and, if so, how much and in what form—pipe, cigar or cigarette. The answer was the same in Britain and in America—nearly all patients with lung cancer smoked heavily, and smoked cigarettes, whereas patients with cancer at other sites included more non-smokers, and among those who did smoke there were more who smoked a pipe. It was shown that these differences were so large that they could not reasonably be ascribed to chance. The experimenters thus found that patients with lung cancer differed in smoking habits from patients with cancer at other sites—the former smoked more and smoked cigarettes rather than pipes; non-smokers were very uncommon among patients with lung cancer.

This epidemiological study has now been followed by observations on human volunteers—the 40,000 doctors who volunteered information on their smoking habits and who are the analogues of the experimental animals sacrificed in the work on β-naphthylamine. The initial results confirm the difference in smoking habits between those who die from lung cancer and those who die from cancer at other sites. Had the stimulus been exposure to some chemical instead of to tobacco, the evidence already accumulated would be ample for the Chief Inspector of Factories to convince his Minister that regulations restricting its use were essential.—I am, etc.,

London, N.W.10. GEORGE DISCOMBE.

Danger of Boric Acid in Dusting Powder

SIR,—In an annotation (*Journal*, July 24, p. 222) you have drawn attention to the danger of applying boric powder to babies with napkin rash. The *National Formulary*, however, requires that when "baby powder" is prescribed conspers. talc. boric., *B.P.C.*, which contains approximately 10% of boric acid, shall be dispensed. Moreover, the purchase tax regulations provide that this dusting powder, and substantially similar dusting powders "which contain not less than 5% of boric acid and for which no toilet claims are made" are eligible for relief from the highest rate of purchase tax. In their effect these two rulings give strong official encouragement to the use of talcs containing boric acid, which your article says "is better not used in infant hygiene."

The U.S. Federal Drug Administration, after extensive investigation of baby talcs, has reported that talcum powders prepared with 5% of boric acid are "safe," but such a statement does not carry the weight of an official pronouncement in this country. In view of the very positive warnings conveyed in your article an early official statement is needed to resolve this anomalous situation.—I am, etc.,

Liverpool. C. W. ROBINSON,
Director, Evans Medical Supplies, Ltd.

REFERENCE

1 *Pharm. J.*, 1954, 172, 138.

SIR,—In the *Journal* of July 24 (p. 222) you published an annotation on "Poisoned Nappies" in which you pointed out the danger of the application of a talcum powder containing boric acid to excoriated skin. If this is so, surely the matter should not be allowed to rest without some further action or recommendations. It is still the common practice to prevent or treat bedsores and other excoriations with surgical spirit and talcum powder, and it would be of great interest to hear your opinion as to whether this practice should continue.

The *National Formulary* lists the preparation conspersus talci borici *B.P.C.*, which is shown as containing 10% of boric acid powder. A footnote states: "When baby-powder is prescribed conspersus talci borici shall be dispensed," the words "baby powder" being replaced by "dusting powder" in later editions. If your assumptions are correct, surely the boric acid content of this powder should be removed. Its presence in this powder is of doubtful benefit, and it is included, I am informed, in order to meet with a

standing Board of Trade requirement that talcum powder containing 5% boric acid powder can be classified as a medicated powder and so pay a lower rate of purchase tax than purely cosmetic powders. In view of your recommendations, surely the Board of Trade should be asked to amend this regulation.—I am, etc.,

London, E.C.2. C. H. HOSKYN.

Obstetric Anaesthesia

SIR,—The high standard of obstetric training in this country that is ensured by the Royal College has eliminated most of the risks from operative obstetrics. The abdominal route is rightly preferred to a difficult and traumatic forceps extraction, while a wide range of techniques and instruments is available for the correction of malpresentations and malpositions of the foetal head. However, there remains the risk from aspiration of acid gastric contents which has been so well revealed by the recent article of Dr. R. B. Parker (*Journal*, July 10, p. 65).

Dr. Parker has pointed out the obvious advantage of local and regional analgesia, and it is surprising to see that this suggestion has not received favourable comment in your columns. Dr. A. H. Morley (*Journal*, July 31, p. 299) offers as an alternative the use of the left lateral position for complicated deliveries and considers that this should be taught to medical students as a standard procedure. The advantage to the obstetrician of the true Sims position, in which incidentally it is remarkably difficult to anaesthetize a patient, is that the presenting part tends to fall away from the pelvis between contractions and when the uterus is relaxed by anaesthesia; this gives additional safety to the baby when the cord is prolapsed and extra room for obstetric manipulations when a leg is to be brought down for an impacted extended breech. During the commoner manœuvres it is more convenient for the presenting part to be as low as possible, and the "wandering" application of Kielland's forceps may be impossible in the Sims position. It should also be remarked that the preservation of complete asepsis is satisfactory only in the lithotomy position.

The routine use of the stomach tube prior to induction as advocated by Dr. E. Godwin (*Journal*, July 31, p. 299) has been tried and abandoned. A narrow tube will fail to remove solid material, while a full-sized tube causes such distress that there will often be significant deterioration in the condition of a patient who may already be bordering upon exhaustion. It represents a most unsatisfactory compromise.

The only disadvantage of local or regional analgesia is the difficulty in learning how to effect it, and a distinction should be drawn between the analgesia required for the low forceps operation and that for a more difficult extraction. The case suitable for the less experienced operator, when a wide area of the head is visible and the occiput is already anterior, may be treated by simple infiltration of any local analgesic into the skin lateral to the vulva and perineum. Provided about 30 ml. is used on each side from the anal sphincter posteriorly to the clitoris anteriorly, the forceps may be applied almost painlessly. The injection may be made during the second stage of labour, while there is still doubt as to whether an episiotomy alone will suffice, and traction should be made on the forceps only while the patient bears down. It is often simple to deliver the child without the mother knowing that her own efforts have been in any way supplemented. For the more difficult delivery, in which the head is at a higher level and some degree of failure of rotation is presumed, considerably more analgesia will be required. For this I formerly advocated a low spinal block, finding no complication beyond occasional headache, though I felt that caudal analgesia would be perfect. With the introduction, however, of lignocaine as a local analgesic agent it has been possible for senior residents and visiting staff to carry out complicated obstetric deliveries with complete satisfaction under bilateral pudendal block in a way that had not previously been achieved with other solutions. I am now convinced that every specialist obstetrician should be trained in this procedure, while every obstetric practitioner should carry a large bottle of the solution for local infiltration whenever the second stage of labour is in any way unsatisfactory.—I am, etc.,

Birmingham. W. G. MILLS.

SIR,—The interesting letter of Dr. A. H. Morley (*Journal*, July 31, p. 299) on obstetric anaesthesia serves to heighten the dilemma confronting many in domiciliary midwifery. Having been trained in hospital over a considerable period to use the lithotomy position, I was soon converted in practice to the use of the lateral, and I can fully endorse his plea for the latter. Without the use of sling or stirrup there can be few advantages in the lithotomy position for delivery. In any case the lateral is undoubtedly the safe position for administering obstetric anaesthesia. The control of the perineum is also easier in the lateral, if, indeed, it is the correct thing to control and "save" a perineum. Here again we require a lead or an explanation of why the tearing of the perineum is encouraged in hospital and discouraged in instructions to domiciliary midwives.

Consultant opinion stresses the value of local analgesia in labour, but is it really practical, and, if so, is it advisable for practitioners to adopt it without a period of instruction and training in its use? The use and choice of anaesthesia has become more important with the epidemic of the "compensation complex" and in particular, perhaps, the use of chloroform. Its merits and demerits have all been fully discussed but not in relation to obstetric anaesthesia. We are all aware of its potency and dangers, but the rules for its safe administration are simple and its limitations clear cut. If our conduct of manipulative obstetrics is wise anaesthesia will be of comparatively short duration, and is there any real evidence that a short, well-administered chloroform anaesthesia is any more harmful to mother or foetus than the general anaesthesia? We get little help from the textbooks, apart from vague references—for example, chloroform anaesthesia for labour should not be lightly discarded, etc.—and in general it has been stated that the problem is not choice of anaesthetic but choice of anaesthetist.

The important question is: what will be the attitude of the coroner in a maternal death in which chloroform was used? The coroner must be influenced only by current published medical opinion. Should the present "chloroform fans" (convinced that it is usually the most suitable obstetric anaesthetic) cease using it? Is there, in fact, statistical evidence that chloroform has proved more dangerous than others in obstetric use? This is an everyday problem, and published opinion would be a great help, as, indeed, many excellent articles on obstetrics have proved during the past year—for example, "The Place of Forceps in Present-day Obstetrics," by Professor T. N. A. Jeffcoate (*Journal*, October 31, 1953, p. 951). We seem to have reached agreement on the safe limits for domiciliary manipulative obstetrics, and it would be a great comfort to establish a similar position in obstetric anaesthesia.—I am, etc.,

Sheffield. ANDREW STEPHEN.

Probe as Intramedullary Splint

SIR,—The following case is of interest as it illustrates the use of an ordinary probe as an intramedullary splint at a small hospital where appliances for bone surgery were limited.

A woman aged about 28 was attacked on March 3, 1954, by a man with a heavy cutlass. She sustained numerous very severe lacerated wounds, including a deep wound of the right arm and forearm severing the radius, the common extensor origin, and the musculo-spiral nerve. The fragments could not be kept in position without mechanical fixation, and, as nothing else was available, part of a probe was used as an intramedullary splint. Four months later x-ray examination showed that strong bony union had occurred. The wound has healed, but further operative treatment will be necessary to provide means of dorsiflexion of the wrist and fingers, this being limited on account of the nerve paralysis.—I am, etc.,

Akwatia, Gold Coast. S. V. HUMPHRIES.

Danger of Surf-bathing

SIR,—While everyone must feel deep sympathy for Dr. C. Langton Hewer (*Journal*, August 7, p. 358) in his predicament—that is, the expert in face of an emergency without his proper tools—it is unlikely that the bathing beaches of the West Coast could be equipped for all the changes and chances of this mortal life—for example, amputation of a limb by a shark, or acute anaphylaxis following the sting of a jelly fish. It was said of a distinguished laryngologist from Dr. Langton Hewer's own hospital that he saved life in a restaurant by an emergency tracheotomy with the aid of a tableknife and a hairpin.—I am, etc.,

Sherborne. JOHN WHITTINGDALE.

Prevention of Congenital Syphilis

SIR,—Dr. Joseph Barnes's letter (*Journal*, July 24, p. 242) criticizes my article on the prevention of congenital syphilis (*Journal*, June 26, p. 1470) on the grounds that the diagnosis of antenatal latent specific disease is not justified by the findings and confirmation of positive serological tests. He also regrets that no mention was made of false positive reactions. Dr. Barnes seems very confident that the treponemal immobilization test, the results of the husband's W.R., and post-partum tests on the women concerned would contribute to the making of a firm diagnosis antenatally.

He may be assured that all these aspects receive attention, not only by myself but by all venereologists of my acquaintance. When, however, these aspects are examined individually, do we in fact find that Dr. Barnes's confidence is well placed? The true value of the treponemal immobilization test is as yet not fully established. It is generally agreed that once positive it will remain positive for many years, but it is not known whether it gives immunity to the occurrence of false positive serological tests. Further, because a husband admits treatment for syphilis, or because a husband has an asymptomatic positive Wassermann reaction, this does not really help to unravel the pregnant wife's serological problem. As for Dr. Barnes's third suggestion, that we should wait until after delivery before making a diagnosis, this leads me particularly to feel that he does not face the problem of the prevention of congenital syphilis with any real seriousness. All these suggestions, however much they may contribute, do so only circumstantially, and full reliance for the diagnosis of latent syphilis must therefore be placed in confirmed positive findings serologically. If results are strongly positive—that is, if the Wassermann is positive in high or diagnostic titre—no doubt should be entertained as to the true diagnosis.

Few aspects of syphilis control have produced a greater mass of literature than that which has accumulated on the false positive, W.R., Kahn, etc. So-called false positive reactions usually fall into the range of "doubtful" titres. It is then that Dr. Barnes's suggestions, together with the patient's history, the finding of syphilitic scars, and particularly whether any antibiotic therapy has been given at any time, should all receive consideration. In such cases the diagnosis, whether of syphilis or non-syphilis, is often highly circumstantial, and is quite different from the cases mentioned above, where the diagnosis is certainly beyond reasonable doubt.—I am, etc.,

Stockport. R. S. MORTON.

Coagulation Defect in Accidental Haemorrhage

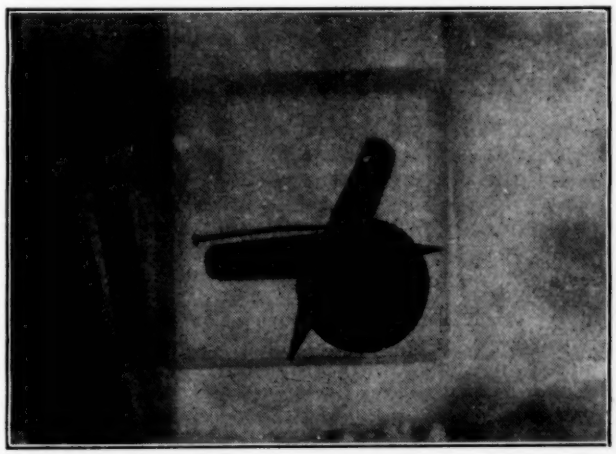
SIR,—In his interesting report dealing with the coagulation defect sometimes seen in association with accidental antepartum haemorrhage (*Journal*, July 31, p. 277) Dr. H. C. Moore is unwittingly somewhat ungenerous towards his obstetrical colleagues in Dublin. He states that in spite of the obvious importance of this complication little or no attention has been paid to it in the British literature, but overlooks the fact that Barry in his Annual Clinical Report from the National Maternity Hospital has dealt with the problem in some detail in each of three successive years (1951, 1952, 1953). Readers who visited the Scientific Exhibition held during the Annual Meeting at Cardiff in 1953 may possibly recall Dr. Barry's exhibit dealing with accidental haemorrhage in which the recognition and management of this coagulation defect formed a main theme. In his most recent clinical report (1953) Barry alludes also to the fact (now well established) that a similar fibrinogenopenia may be encountered in cases of retention of a dead foetus in utero and in association with amniotic fluid embolism.—I am, etc.,

Dublin, C.5. FRANK GEOGHEGAN.

An Early X-ray Picture

SIR,—There has recently come into my hands an *x*-ray photograph (here reproduced) which was taken in Hanover during the Easter of 1896. I am indebted to Colonel W. E. Davies, who took the picture, for allowing me to place on record the details. Colonel Davies, then a boy of 16, was sent in March, 1896, to Hanover for the Easter holidays, to learn German in the home of General von Sothen.

Colonel Davies writes: "I was a schoolboy photographer of considerably less than mediocre merit. My camera was a black box, taking quarter plates. One of the entertainments at Hanover was a hall with 'shows,' automatic machines, and the like. One was an automatic *x*-ray machine. As I remember the instrument, it was a square pedestal, chest high, and about 18 in. square. On the top was an eyepiece to look through. Below was a slot in which you put your hand or anything else. You put a pfennig in the slot, the *x*-rays were turned on, and you saw the bones of your hand.



"I was interested, and in the dark of the night I put one of my quarter plates (Ilford I think) wrapped up in paper in an empty plate box. The boxes, as I remember them, were square black cardboard, with a label on top. The plates were wrapped in thin brown paper and all was light-tight. I filled up the box with various items such as a coin, a pen nib, a sort of celluloid cigarette case, and my keys. The whole lot was well padded out with paper and the box shut up. Next day I put it into the machine and put in one or more pfennigs. The exposure was about one minute.

"When I got home I developed the plate in the dark corridor between my elder brother's bedroom and my own. The supply of water was by jug, the waste by slop pail. The developing and fixing were sufficiently successful to justify printing. The negative was put in a wooden frame with a piece of, I think, Ilford P.O.P. It was exposed to the light, toned, fixed, and washed."

Apart from the interest attaching to the date of this *x*-ray picture, only a few months after Roentgen's original experiments, there are, I think, two noteworthy points. It is remarkable that "show business" should so quickly adapt this new scientific discovery for entertainment purposes, and in such a dangerous form of peep-show. It is also much to Colonel Davies's credit that he, when a schoolboy, should show such a spirit of scientific curiosity.—I am, etc.,

London, W.1. S. COCHRANE SHANKS.

A Mouthful of Wire

SIR,—Miss Mabel Carter (*Journal*, August 7, p. 361), in invoking the opinion of the medical profession on the frustration, irritation, and despair occasioned by her charges' wearing of orthodontic appliances, may well find herself in difficulty, as this specialty of a specialty, to wit dentistry, taxes all the powers of clear thinking of dentists themselves, much more so their medical colleagues. The matter, incidentally, has a wider import, as orthodontic treatment can be given as part of the National Health Service, and it is imperative that public money be spent to good advantage: the powers that be have long given the matter close attention, and at times, no doubt, have experienced a measure of the emotions which have so powerfully affected your contributor to the *Journal*.

At the risk of over-simplification a plain question may be enlightening; what is Miss Carter, as any parent, to do when some young thing for whom they are responsible proceeds to grow teeth so irregular as to be a travesty of normality, a source of ridicule, or an obstacle to matrimony, or produce jaws so badly aligned and inefficient in the masticatory sense as, in some instances, to make the owner invariably last at the meal table? The aid of the dentist is naturally invoked, who will, by and large, find himself confronted by one, or all, of three main types of abnormality. First, pure irregularity of the teeth themselves in varying degrees of severity, arising as a simple mechanical result of lack of overall space. In such cases planned extractions at the appropriate time, and appliances of the simplest nature, give first-rate results with complete long-term stability. Secondly, irregularity of teeth due to faults in position and subsequent growth of the tooth germs themselves. These cases can be controlled with appliances, often of greater complexity than those used for the first group, but a risk of later relapse and incomplete long-term stability; for such cases extraction of tooth units may well not be required, though removal of any grossly misplaced tooth may obviate a long and tiresome phase of appliance wearing. Thirdly, faults in the jaw structure itself. For all such cases prolonged treatment is required if the basic pattern is to be broken up or otherwise modified, so that an acceptable result can be secured, and it would be only fair to say that the best brains in the dental profession are divided as to how the most desirable results are to be achieved.

Almost every regime of treatment requires a corrective appliance of some sort, and, as only delicate motivating forces are safe to employ, the appliances themselves cannot always have the rugged and crash-proof robustness that is so desirable for active youngsters. Scholastic conditions, *pace* your contributor, do not make the dentists' work more easy, as it is considered desirable, and is certainly fashionable, to send children as far from their homes as their parents' purses will allow, and the possibility of strict follow-up by the dentist planning the case is often limited, to the detriment of all concerned. It is difficult, therefore, to see how Miss Carter's burden can be lightened, and we can only hope that in the future the dentists attending her charges will be men who have a sure and certain instinct for selecting cases they know will improve by simple treatment, and for all other cases making it wholly clear to the parents just what is involved if the benefits of treatment, so earnestly desired, are to be brought within bounds of a reasonable probability.—I am, etc.,

London, S.W.1. ROBERT CUTLER.

SIR,—Your correspondent, Miss Mabel Carter, who is headmistress of a school near Wirral, asks (*Journal*, August 7, p. 361) for the opinion of the medical profession concerning what she mistakenly terms "the new craze for filling children's mouths with plates and plastic or metal contraptions in order to straighten teeth or alter the shape of the jaw."

The practice of orthodontics was already well established during the latter part of the nineteenth century, principally as a result of the work of Dr. Angle in the United States, whose pioneer investigations in this field have been developed into a definite specialty which is already recognized in this country by the Diploma in Dental Orthopaedics at Glasgow, and the institution in the near future by the Royal College of Surgeons of England of a Diploma in Orthodontics. There is therefore little that is new regarding the conception of this method of treatment, and it would hardly seem to justify the term "craze."

I feel that Miss Carter is somewhat confused in her sense of values when she refers to the children at her school being "afflicted" by the wearing of orthodontic appliances. Surely it would be more reasonable to state that they are wearing these appliances *because* they are afflicted?

Mankind has a definite conception of what constitutes facial harmony, although this does vary considerably from one race to the other. The broad trend of evolution is to shorten the projection of the jaws below the base of the cranium, but it is still true to say that such shortening should be balanced evenly between the upper and lower jaw and that any gross degree of projection of one in relation to the other is displeasing, creating in the public mind mental associations more in keeping with "Popeye the Sailor" or the vacuous "Bertie Wooster." We are all a complex mixture of genes, and the heritage which we receive from our parents in this manner may result in the eruption of large teeth in small jaws, and *vice versa*, and the development, according to some authorities, of faulty muscular patterns of mastication and swallowing, aggravated by unfortunate habits of thumb and finger sucking.

Whilst I sympathize with Miss Carter over the interference with her carefully planned curriculum resulting from the routine visits which are necessary to ensure that orthodontic treatment is proceeding according to plan, I feel that she is lacking in a sense of proportion when she asks if such treatment "is really necessary." Disproportionately shaped jaws, with narrow arches and overcrowded irregular and projecting teeth, predispose their owner to caries, and the appearance can hardly be said to enhance the prospects of marriage for the girl or promotion for the boy when school-days are over and the outside world has to be faced. Although Miss Carter may feel that a mastery of irregular verbs should take precedence over the orthodontist's mastery of the irregular teeth, she might take heed of the words of Herrick in the *Hesperides*: "Art quickens nature; care will make a face; neglected beauty perisheth apace."—I am, etc.,

Andover. N. L. ROWE.

Protection of Teeth During Laryngoscopy

SIR,—In 1934 Colonel G. F. O. Alley, in the Royal Army Medical Corps, taught me to protect patients' teeth from trauma with a laryngoscope during intubation by placing a strip of lead over the teeth. Since then I have found it convenient to make protectors out of lead-covered telephone cable. In use the protector is placed over the centrals and left lateral incisors with the left hand and held in place with the left forefinger while the blade of the laryngoscope is glided into position.

This protector has an advantage over those attached to the laryngoscope in that it helps to support a loose tooth against firmer brethren and distributes pressure, thereby making dislodgment less liable to occur.—I am, etc.,

Northallerton. J. SHEGOG RUDDELL.

Milli-equivalents

SIR,—From your annotation (*Journal*, January 23, p. 205) it appears that you have realized the difficulty of a large number of medical men about understanding the reasons for adopting milli-equivalents in preference to the orthodox mg. % as a measure in describing the strengths of solutions. You mention "special features" that make them preferable to use in the estimation of the electrolytes of the plasma, without explaining them. As you have said, "fluctuations in concentrations of electrolytes" may have "some

meaning" in relation to each other, but one is left in the dark as to how it helps the medical man in the treatment of the patient. To me, as perhaps to many others, "milli-equivalents" is an unnecessary, pedagogic, esoteric nomenclature introduced to replace a simpler and more useful one. I will be grateful for any light on the problem from a practical point of view that will help me to correct my understanding if it is wrong.—I am, etc.,

Poona City, India. P. L. DESHMUKH.

Enormous Scrotal Herniae

SIR,—For some time now there has been something near excitement in the *Journal* over the finding of an appendix in a hernial sac. Here in Nigeria, where I practise, it is frequently seen. I sincerely wish some of our colleagues could come out here and be face to face with the disarming discovery of patients who have for a long time come to regard diseases, including hernia, as "natural occurrences."

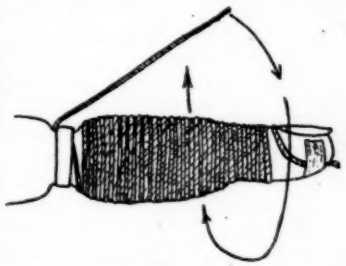
As far as hernia is concerned, my experience here is that what brings patients to the doctor is not the appearance of a swelling in the groin but the fact that they have been taken off their feet by the extreme size of a scrotal weight. As would be expected, a majority of these large hernias is sliding, dragging all the movable abdominal organs through an extremely large internal ring into the scrotum, leaving the abdomen flat, and difficult to reduce. On the left, the more frequent organs are the bladder and coils of the large and small intestines, while on the right the only viscus I have not found in the scrotum is the liver! Owing to the large size of the aperture, strangulation is comparatively rare. Of the 404 hernias I have done here in the last four years (223 right and 181 left), only 28 were strangulated.

In some parts of the world where patients are more "understanding," one might safely label these herniae inoperable, but if any doctor made that decision twice in six months here, nutritional oedema of the ankles would warn him that it was time he left the area.—I am, etc.,

Irrua, Nigeria. XTO. G. OKOJIE.

Ring Incorporated in Finger

SIR,—The recent correspondence (*Journal*, May 22, p. 1210, and July 17, p. 173) concerning rings incorporated in the finger prompts me to describe a simple method—not, I believe, widely known—of removing a ring from an oedematous finger before it has actually become incorporated in the soft tissues. The method has the advantage of removing the ring intact, without the necessity of cutting it. This point is usually appreciated by the patient, and I have even known a patient refuse to have a ring cut off despite a warning that its retention might mean the loss of the digit.



A small aneurysm needle, lubricated with soap or cetrimide, is passed proximo-distally beneath the ring, and one end of a piece of fine twine or stout ligature silk is drawn back beneath the ring to the proximal side. The long end of the silk is then wound with the turns close to each other all the way to the tip of the finger, where the distal end is temporarily attached by a small piece of zinc-oxide plaster. The proximal end of the silk is then angulated as shown in the sketch and rotated round the finger so as to undo the spiral. It will be appreciated that not only is the ring pulled distally over the soft tissues, but that the soft tissues are milked proximally beneath the ring as each turn of the spiral is unwound. Provided there has been no underlying bony enlargement, it is possible to remove a ring by this method no matter how oedematous the soft tissues may be.—I am, etc.,

Sheffield. I. J. MACQUEEN.

Obituary

Sir STANLEY HEWETT, K.C.B., K.C.V.O.
K.B.E., M.D., L.S.A.

We record with regret the death on August 11 of Sir Stanley Hewett, Extra Surgeon Apothecary to the Queen. He was 74 years of age.

In a letter to Lord Knutsford of the London Hospital early in 1929, when the serious illness of King George V, which had preoccupied the nation for some months, was taking a more favourable turn, Lord Dawson of Penn wrote, "Stanley Hewett has been very good throughout, nobody could have been better." That was a tribute from the King's chief physician to the King's surgeon-apothecary, and it could have been paid at all times to Sir Stanley Hewett during his long service at court. He was invariably kind, tactful, and self-effacing, but, when necessary, was ready to be forthright in giving advice and firm in sticking to his opinion. It is true that he had the advantage of attending a Royal Family who were free from many of the stilted conventions which governed royal residences in earlier times, and which must have imposed extraordinary restraints and difficulties on the medical household. He was able to go about his work at Buckingham Palace and elsewhere with the quiet efficiency which usually marks the family doctor, and he made many friendships among his patients. He served in the medical household during four reigns, altogether for some 43 years—a longer period of service than that of Lord Dawson himself, who served for 38 years.

Frederick Stanley Hewett was born in Weybridge, in Surrey, on May 26, 1880, the son of Frederick Hewett, who died only a few years ago at Hythe, near Southampton. From Haileybury School he went up to Caius College, Cambridge, and continued his medical education at St. Thomas's Hospital. He qualified in 1905, graduated M.B., B.Chir. in 1906, and proceeded M.D. in 1910. After serving in a number of house appointments at St. Thomas's, including the post of senior obstetric house-physician, and also at the West London Hospital, he joined the staff of the Victoria Hospital for Children, Chelsea, as an anaesthetist. In 1911 he received his first court appointment as deputy surgeon-apothecary to King George V. When Sir Francis Laking, who held the senior post, died in 1914 Hewett succeeded him as surgeon-apothecary. During the first world war he served as surgeon lieutenant-commander, R.N.V.R.

Soon he settled down to what proved to be a lifelong career in the royal service, residing in Cleveland Row, just under the tower of St. James's Palace. His official address in the *Medical Register* was Stable Yard, St. James's, but the address meant no denigration of the position of surgeon-apothecary such as was current a hundred years ago, when Queen Victoria would command "the gentlemen and Mr. Reid" to attend in the

drawing-room. Hewett was also appointed surgeon-apothecary to Queen Alexandra's household, and he served that gracious lady until her death in 1925. In 1923 he became surgeon-apothecary to the Prince of Wales and his household, and remained in that office during the short reign of Edward VIII. After the death of George V he became surgeon-apothecary to Queen Mary. In 1937, with the new reign, his appointment as surgeon-apothecary to George VI and his household was announced, continuing until 1949, when he became extra surgeon-apothecary to the King and to the royal household and again to the present Queen. He was succeeded as surgeon-apothecary by Dr. J. N. Loring in 1949.

It may be explained that certain appointments "to the household" are now full-time posts paid for out of the Civil List. These posts carry responsibility for the medical care of the whole staff at one or other royal residence. Other posts are honorary or carry a retaining fee, and for personal attendance on the sovereign payment may be made out of the privy purse, and nothing appears in the published figures. The position of surgeon-apothecary, which is really that of family doctor to the royal household, to some extent fetters professional freedom, with the result that Hewett seldom put in an appearance at medical gatherings, while to the public he was just a name on a bulletin. It does not appear that he contributed anything to medical literature, and he certainly made no excursions into medical controversies. He never sought public occasions. The only outward and visible honour which he seems to have received from his professional brethren was in 1931, when the Society of Apothecaries of London, always feeling a certain pride in the old-world title of "apothecary" which lingers on in the royal household, and mindful of the fact that it was an apothecary to James I who was the means of obtaining the charter of the Society, conferred on him its honorary diploma, an honour which it repeated in the case of his successor, Dr. Loring, a few weeks ago.

The surgeon-apothecary, or general practitioner to the Royal Family, carries a great responsibility. It is he who must always be alive to any indications of ill-health in the illustrious persons whom he has in charge, and know when to call in advice and assistance without creating public alarm or interfering with the routine of court. It was thus that Stanley Hewett had occasion in November, 1928, to summon Lord Dawson to the palace when he felt that something was seriously wrong with George V, presaging his long illness. It was thus, too, that his predecessor in office, Sir Francis Laking, refused to leave the room until Edward VII had consented that Sir Frederick Treves, the surgeon, be summoned, and Treves told the King that if he tried to go through with the coronation, fixed for two days ahead, he would probably die. For more than a generation, as has been said, "Stanley Hewett" to the public was a name on a bulletin. Sometimes the bulletins contained announcements which gave occasion for national rejoicing, such as the birth of a prince or the recovery of a monarch from a grave illness; sometimes they plunged the nation into anxiety or mourning. The most famous of the bulletins to which his was one of the three names attached was the one issued on January 20, 1936, "The King's life is moving peacefully towards its close."

Hewett was always cheerful, modest, and ready to help. The Royal Family and household had by long experience come to trust and value him highly, and his long service and constant devotion won him scores of admirers in the royal circle. For his services he was made K.C.B. in June, 1929. He had previously been made a Member of the Victorian Order in 1916, K.C.V.O. in 1921, and K.B.E. in 1926. On his retirement he went to live only a few hundred yards from the palace gates, in Mount Street, where he died after only a few days' illness. He was unmarried.

We are indebted to Dr. Nigel Loring for the following appreciation: To many who knew him and valued his friendship, the passing of Sir Stanley Hewett will seem to mark the closing of an era—an era that bred men of character and distinction, uncompromising in their likes and dislikes and ready to champion their friends or trounce those of whom they disapproved with equal gusto—men who "walk uncowed by fear or favour of the crowd." When such men, as was the case with Sir Stanley, are shrewd judges of character, their friendship is indeed valued, and in my own case, after twenty-two years of acting as his substitute and five years as his successor, I find it difficult to realize that my old friend is no longer with us.

Sir Stanley succeeded Sir Francis Laking as apothecary to the Royal Household towards the beginning of the reign of George V, and quickly established himself as the friend and adviser of all those who came under his care. In his capacity as Surgeon-Apothecary to King George V and the late Queen Mary he occupied a position of responsibility for which he was admirably fitted by his wisdom, his unswerving honesty, and his never-failing cheerfulness. And it is, perhaps, by this last—his cheerfulness—that many will best remember him. "I suppose it is because he has had the sense to remain a bachelor," one of his lady patients once remarked to me. But whatever the reason, it could be truly said of him that those who were privileged to meet him were the better for having done so, for he left behind him a feeling of cheerfulness which seasoned the soundness of his judgments and was a source of comfort and encouragement to the many grateful patients and friends who will mourn his passing.

Dr. Desmond MacManus writes: The passing of Stanley Hewett has left a great gap and sense of loss among his host of friends. Apart from the unique position which he made for himself as a doctor to royalty he had a very good general practice which could have become an enormous one had he so desired. In his earlier days he was keen on obstetrics, and was a very good accoucheur. In later years he complained that the children he brought into the world would pester him to do the same for them after they had married. Without being brilliant he had the most robust common sense, and his advice was sought by many in all sorts of difficulties—not necessarily medical. His flat was a small museum, housing the many gifts he had received through his long career from the royalties of many nations and other famous personages; and he was a wonderful host.

It was in the field of sport that he was happiest; a good cricketer in his youth, he gave it up owing to the call of medicine. Golf and shooting were his two loves. At golf, though short, he was so straight and so difficult to beat. Littlestone—where he will be greatly missed—was his spiritual golfing home. And he loved the fleshpots—the good dinner and his glass of port—where his conversation was always witty and cheerful. How many have I shared with him! Stanley has gone, but the memory of a great gentleman and a great sportsman remains.

Sir FRANK CONNOR, D.S.O., F.R.C.S.

Sir Frank Connor, who died on August 8 at the age of 76, held for over a quarter of a century an outstanding position as a general and consulting surgeon in Calcutta and north-east India. His capacity as an operator, his ability as a teacher, and his sympathetic approach to patients gained the complete confidence of the public, European and Indian alike. His death

will be widely mourned over the great area where his former pupils now practise.

Born on September 16, 1877, the son of James Connor, of the Survey of India, Frank Powell Connor received his school and early medical education in India. Coming to England to complete his studies for a British qualification, he entered St. Bartholomew's Hospital, where he won the Brackenbury surgical scholarship, and took the London conjoint diploma in 1901. Admitted F.R.C.S. in 1902, he passed into the Indian Medical Service by examination in the same year. After the usual preliminary period of military service, his qualifications and surgical ability secured for him the key post of resident surgical officer of the Medical College Hospital, Calcutta, where he remained for three years. He was then transferred to Bihar, where he had charge of the Gaya and other major civil surgeoncies. The years spent as a civil surgeon with wide opportunities to practise all branches of surgery, including ophthalmology and gynaecology, greatly broadened his surgical outlook. In 1913 he took the D.T.M.&H., and in the following year returned to military duty on the outbreak of the first world war. After a period of service in France and England with Indian troops, he served as consulting surgeon to the Army in Mesopotamia, mostly in the Basra area. He was mentioned in dispatches four times and was awarded a brevet lieutenant-colonelcy and the D.S.O.

After the war Connor resumed his work in Calcutta —teaching, writing, consulting, and operating. As an operator he commanded the respect of colleagues, pupils, and patients, and he acquired an enormous consulting practice. As professor of surgery at the Bengal Medical College, Calcutta, as a Fellow of his university, as a member of the Syndicate of Calcutta University, and as an examiner, Connor played a very full part in the academic field. Towards the end of his time in Calcutta he acted as a visitor for the All-India Medical Council—of which he was president for a short time in 1935–6—to the examinations of various licensing bodies. A member of the British Medical Association for over 50 years, he was president of the South India and Madras Branch from 1934 to 1938. He represented the Branch at two Annual Representative Meetings—Dublin in 1933 and Oxford in 1936.

As he approached the retiring age for lieutenant-colonels, Connor elected to return to military duty to secure promotion which would extend his service in India. After a brief period of command of the military hospital at Quetta he was promoted colonel as A.D.M.S. of the Bombay military district. He was subsequently re-transferred to more suitable employment on the civil side of the Service which he had long adorned. As Surgeon-General of Madras Presidency, with the rank of major-general, Connor's outstanding professional position and work commanded the respect of ministers, politicians, and of the Indian medical profession. In difficult times he managed his department with skill and diplomacy. For some months he acted as Director-General of the Indian Medical Service in a leave vacancy.

The author of a standard textbook, *Surgery in the Tropics*, Connor also contributed the sections on tropical surgery to Rose and Carless's *Manual of Surgery* and other familiar works. He was created a knight in 1926, and appointed Honorary Surgeon to the Viceroy of India in 1932 and to the King in 1934. He retired in 1937.

Sir Frank Connor married Miss Grace E. Lees in 1921, and she survives him together with one son. To them we extend our sympathy.

H. K. CORKILL, O.B.E., M.B., F.R.C.S.Ed., F.R.A.C.S.

Surgeon Captain H. K. Corkill, formerly Director of the New Zealand Naval Medical Services, died at Wellington, New Zealand, the city of his birth, on August 8.

Born in 1897, Harold Keith Corkill was educated at Wellington College and at Edinburgh University, where he graduated M.B., Ch.B. in 1922, his medical studies having been interrupted by service in the Royal Field Artillery from 1917 to 1919. After graduation he held the appointment of house-surgeon at Edinburgh Royal Infirmary and then went to Washington University, where he spent a year as surgical assistant, returning to Edinburgh to become tutor in clinical surgery in the university in 1924–5. In the latter year he obtained the F.R.C.S.Ed., and married Miss Isabella H. Allan, who also graduated in medicine at Edinburgh in 1922. He returned to New Zealand in 1926 and settled in practice at Wellington, where he soon built up a reputation as a general surgeon. For many years he was on the honorary staff of Wellington Hospital, ultimately becoming senior surgeon. Two years ago he published in the *New Zealand Medical Journal* an interesting description of early neurosurgery in that country.

A member of the R.N.V.R. and, later, the R.N.Z.N.V.R. for many years, Corkill was principal medical officer of the Wellington division in 1928–9. He was also port health officer and naval surgeon and agent. Throughout the last war he served in the Royal New Zealand Navy, for a time in the *Achilles*, which, it will be recalled, was one of the three British ships engaged in the successful action against the *Graf Spee* in December, 1939. From 1941 to 1946 he was Director of the New Zealand Naval Medical Services, and from 1941 to 1944 Honorary Surgeon to the Governor-General of the Dominion. Appointed O.B.E. in 1942, he had previously been awarded the Volunteer Decoration. In 1946 he was appointed an Officer of the Order of St. John of Jerusalem. He is survived by his widow, by whom he had one son and two daughters.

L. J. MOORMAN, M.D.

Professor L. J. Moorman, who died at Oklahoma City on August 2 at the age of 79, was a distinguished and beloved figure in American medicine.

Lewis Jefferson Moorman was born at Leitchfield, Kentucky, on February 9, 1875. He graduated M.D. at Louisville Medical College in 1901, and subsequently spent some time in Vienna on postgraduate studies. After a period of general practice in the prairie country of Oklahoma, which he described with graphic charm in his autobiography *Pioneer Doctor* (1951), he began to teach medicine at the University of Oklahoma School of Medicine in 1910, serving as professor of clinical medicine from 1926 to 1935, and as dean from 1931 to 1935. Made emeritus professor in 1947, he lectured on the history of medicine. For 25 years he was medical director of the Moorman Farm Sanatorium. His many honours included the presidency of the Oklahoma County Medical Society (1918), Oklahoma State Medical Society (1920), Oklahoma City Academy of Medicine (1922), Southern Medical Association (1932), American Trudeau Society (1940), and American Medical Writers'

Association (1953). He had been a member of the board of directors of the National Tuberculosis Association from 1920, and was its president in 1943–4. For the last ten years he has been Editor-in-Chief of the *Journal of the Oklahoma State Medical Association*. In 1949 he was chairman of the American Medical Association's team which reported on the health of the Navajo-Hopi Indians.

A voluminous and elegant writer, he contributed numerous articles on tuberculosis and on medical history to the journals and wrote several books, the best-known of which is *Tuberculosis and Genius* (1940, reprinted 1950). Scholar, physician, philosopher, and kindly gentleman, Professor Moorman will be sadly missed by his many friends in this country.—W. R. B.

By the untimely death of Dr. GEORGE (GERALD) BELLMAN on April 24 at the age of 48 while on holiday in Portugal the Charing Cross Hospital and its medical school have lost the services not only of a skilful and reliable anaesthetist but also of a keen and perceptive intellect possessed by one whose advice and help in organization and on committees was much appreciated by his colleagues. Born at Kirsanov, Russia, on May 8, 1905, Gerald Bellman came to England at the age of 7 and received his early education at schools at Brighton. Scholarships took him to King's College, London, and in 1925 he won the senior university entrance scholarship to St. George's Hospital. He qualified M.R.C.S., L.R.C.P. in 1928, and, after a period of general practice in the West End of London and near Regent's Park, he became interested in anaesthetics and was appointed to the staff of St. Mary's Hospital, Plaistow, and of Queen Mary's Hospital, West Ham. During the last war he was anaesthetist to the Emergency Medical Service at the Ashridge branch of Charing Cross Hospital, later joining the staff of that hospital and of the Hendon District Hospital and the Metropolitan Ear, Nose, and Throat Hospital. He was also a member of the board of governors of the National Temperance Hospital and of the Westminster Dispensary. In addition he was reading for the Bar. He took his D.A. in 1943 and became F.F.A. R.C.S. last year. In recent years his work had been frequently interrupted by ill-health, against which he struggled with a determination and persistence which won the admiration of all. He leaves a widow and daughter, to whom we extend our deepest sympathy.—R. J. C.

Dr. HOWARD DITTRICK, medical historian and editor, died at Cleveland, Ohio, on July 11, at the age of 77, of carcinoma of the colon. Born in Canada on February 14, 1877, he was educated at the Collegiate Institute, St. Catharine's, Ontario, and at the University of Toronto Medical School. He graduated M.B. in 1900, proceeded to M.D. in 1927, and did postgraduate work in gynaecology at Vienna, Bologna, Budapest, Munich, and Baltimore. Settling in the United States, he took up gynaecology at Cleveland and was appointed to the staff of Lakeside Hospital. Retiring from private practice in 1943, he became director of the Cleveland Clinic's editorial department. For several years he edited the *Bulletin of the Cleveland Academy of Medicine*, and at the time of his death was directing editor of *Current Researches in Anesthesia and Analgesia*. He was president of the Ohio Academy of Medical History and honorary vice-president of the Medical Library Association. Dr. Dittrick's greatest and most enduring contribution to medical history was his foundation in 1926 of the Howard Dittrick Museum of Historical Medicine, housed in the Cleveland Medical Library Association. One of the largest medico-historical institutions in the United States to-day, it is specially rich in material illustrating pioneer medicine in the Western Reserve. Dr. and Mrs. Dittrick travelled far and wide in search of specimens, and one of their finest and most complete collections is one depicting the history of nursing bottles. Dr. Dittrick delighted in showing visitors round his museum, and there must be many British doctors who will treasure the memory of an indefatigable guide who wore his learning lightly and taught medical history in charmingly anecdotal fashion.—W. R. B.

By the death on June 23 of Dr. T. P. O'LOUGHLIN Wolverhampton has lost a greatly respected medical man who was known and liked far beyond the bounds of his practice. Thomas Patrick O'Loughlin was born at Mitchelstown, Co. Cork, on March 2, 1897, and received his early education at Blackrock College, Dublin. In 1920 he qualified L.R.C.P.&S.I. at the Royal Colleges in Dublin, and then went to Wolverhampton as assistant to his uncle, the late Dr. W. P. McGrenahan. Shortly afterwards he became medical officer to the board of guardians, and in 1927 commenced practice in the Penn district of the town. Last year he and Mrs. O'Loughlin were injured in a motor accident, and a period of ill-health followed so that he was unable to resume whole-time practice; yet his death was sudden and unexpected. There was nothing neutral about Dr. O'Loughlin. His arresting personality cheered and fortified his patients. His opinions were always worth listening to, and his views on life and art, food or travel, enlivened and stimulated many a happy party in his own home or elsewhere. He was a splendid host, with a fund of stories always at his command. A very large congregation assembled for the requiem mass at St. Michael's church to mourn his end and to express sympathy with his widow and two sons.—R. L. M.

Dr. DOUGLAS GREEN died in Sheffield Royal Infirmary on July 25 at the age of 67, in the same room he had occupied when he was the resident surgical officer there more than forty years ago. Douglas Green was born on December 18, 1886, a member of a well-known Ecclesfield family. From the Grammar School at Barnsley he obtained the open scholarship to the medical school of Sheffield University as well as a major county scholarship. He had a distinguished career as a student, not merely excelling in scholastic attainments but also showing keen interest in games, especially Association football, and in the social life of the medical school. He obtained distinction and the scholarship in physiology in the intermediate examination of London University and graduated M.B., B.S. in 1910. He then became a member of the resident medical staff at Sheffield Royal Infirmary for three years, being resident surgical officer during his final year. His professional inclination was towards a surgical career, and he accepted a resident post at St. Luke's Hospital in London, attended a postgraduate course at University College Hospital, and obtained the diploma of Fellow of the Royal College of Surgeons of England in 1914. He then spent a year making several trips to the Far East as a ship surgeon. He joined the R.A.M.C. during the first world war and served in France and the Midde East as a regimental medical officer. Dr. Green finally settled in the Woodseats district of Sheffield as a general practitioner and made himself the beloved physician, counsellor, and friend to a wide circle of patients. He was an extremely good committee man, and his helpful advice and tactful approach to the many problems which have had to be solved during recent years will be greatly missed. His tolerance was such that he could always see the other man's point of view and give him credit for it, and, if convinced, would change his own opinion. During the last war and subsequently his services had been in great demand. He was chairman of the Sheffield Division of the British Medical Association in 1941–2, and for many years had been the charity secretary of the local Division on behalf of the Royal Medical Benevolent Fund and also one of the local stewards of the West Riding Medical Charitable Society. He was also chairman of a pensions board and of a recruiting board. For many years an active member of the Sheffield Medico-Chirurgical Society, he was its president in 1949–50, and at the end of his year of office he presented the Society with a president's collar and badge. His presidential address illustrated his

wide professional interests, his tact and courtesy to all sorts and conditions of his patients, and was flavoured all through with examples of his unfailing and useful sense of humour. His death has removed a well-known personality from the medical circles of Sheffield. Unostentatious in manner, he was by his life and character a great example of the influence which a good general practitioner can exercise in a busy industrial city, which also contains a university and teaching school for medical students. Dr. Green was twice married and is survived by his widow, two daughters, and one son, a solicitor. One of his daughters is a member of the medical profession and the other is senior occupational therapist at the City General Hospital, Sheffield.—J. H. C. and B. F.

Dr. W. W. McGRATH died in the Royal Infirmary at Gloucester on August 4 after a short illness at the early age of 41. William Wilson McGrath was born at Coleraine, in County Derry, on July 1, 1913, and was educated at Coleraine Academical Institution, where he won the Cloth Workers Scholarship. From there he went on to Trinity College, Dublin, and graduated M.B., B.Ch. in 1938. He was a house-surgeon to the eye and ear, nose, and throat departments at the Royal Infirmary, Doncaster, where he met his wife, who was a sister in the same hospital. After a further period as house-surgeon at the Royal Infirmary at Gloucester, he joined the R.A.F. soon after the outbreak of war in 1939. He served with distinction in the North African campaigns as an eye specialist, and in the last year of the war in command of No. 1 R.A.F. Hospital at Naples, when he held the rank of wing commander. After hostilities ceased, he returned to Gloucester, and joined Dr. D. C. Reavell in general practice in the city. Although he had been living in Gloucester for only eight years, Wilson McGrath was very well known in the district and greatly loved. Many people had experience of his great kindness and care. He was most unassuming and modest in manner, and had a general air of quiet competence, throwing himself unsparingly into everything he did. He lived a very busy and full life, and his medical work covered a wide field, as shown by his many appointments: he was medical officer to several business firms in the city and to a child welfare clinic; he worked for the St. John Ambulance Brigade; and he was a member of a subcommittee of the local health authority. He was besides a recognized ophthalmic medical practitioner. He was an active member of the Gloucester Round Table until two years ago. A keen sportsman, he played football for his college and until a year or two ago was well known on the hockey field in Gloucester, and he also played tennis and golf. He was a devoted husband and father and very fond of his home, where he and his wife often entertained their many friends. Wilson McGrath will be greatly missed by his friends, colleagues, and patients, who cannot fail to remember his kindness, his pleasant smile, and his quiet and competent way of getting things done. The sincere sympathy of all his friends is extended to his widow and two young daughters.—D. C. B.

D. C. R. writes: Wilson McGrath and I worked together in Gloucester for eight years. No one could ever have had a more charming, considerate, and conscientious partner. His humour and kindly sense of fun endeared him to all who worked with him and for him. His patients loved him for his quiet sincerity, for his devotion to their welfare and his obvious concern over their suffering. He was indeed the real family doctor in the best tradition of general practitioners. Few men can have made so many friends in so short a time, and his death is a loss that can never be replaced.

W. J. W. writes: My first introduction to Wilson McGrath was when he was my house-surgeon in 1938. He proved to be the best I ever had; and therefore I was determined to make him return to Gloucester if at all possible. Eight years ago he came back to join my old firm in general practice. In the short time he was spared to work with us he earned himself a unique reputation by his obvious vital personality and high religious principles. His cheerfulness and pleasant demeanour were an inspiration to us all.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending July 31 (No. 30) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	14	0	1	0	0	17	2	7	0	
Dysentery	445	51	176	5	0	525	109	107	4	3
Encephalitis, acute	4	0	0	0		5	2	0	0	
Enteric fever:										
Typhoid	3	0	2	1	0	6	1	2	0	
Paratyphoid	8	0	3	0	1	3	0	2(B)	1	
Food-poisoning	253	11		39	0	524	143		1	
Infective enteritis or diarrhoea under 2 years				12	17				27	31
Measles*	3,387	147	54	162	125	5,504	110	158	197	129
Meningococcal infection	34	3	9	4	2	38	4	6	1	1
Ophthalmia neonatorum	33	0	4	0		45	8	9	0	
Pneumonia†	262	17	82	3		315	18	143	4	
Poliomyelitis, acute:										
Paralytic	53	3	} 8	1	3	{ 118	15	} 7	5	5
Non-paralytic	41	2				65	4			
Puerperal fever§	237	28	12	1	0	253	27	15	1	2
Scarlet fever	712	48	86	13	10	1,072	66	149	29	67
Tuberculosis:										
Respiratory	697	78	141	19				135	26	
Non-respiratory	117	14	18	1				22	1	
Whooping-cough	2,000	90	182	15	10	4,407	374	336	44	60

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	1	0	0	0	0	0	0	0		0
Dysentery	0	0		0		0	0			
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0		
Infective enteritis or diarrhoea under 2 years	1	1	1	1	0	10	1	2		1
Influenza	3	0	0	0	1	2	0	0		0
Measles		0	0	0	0		0	0		0
Meningococcal infection		1	0				0	1		
Pneumonia	119	17	9	10	2	100	15	9		5
Poliomyelitis, acute	3	0			0	8	2			0
Scarlet fever		0	0	0	0		0	0		0
Tuberculosis:										
Respiratory	} 80	{ 7	11	1	4	} 79	{ 5	13		7
Non-respiratory		2	11	0	0		2	2		0
Whooping-cough	2	0	0	0	1	1	0	1		0
Deaths 0–1 year	179	17	23	12	17	176	12	31		16
Deaths (excluding stillbirths)	4,297	565	528	99	143	3,985	557	509		141
LIVE BIRTHS	7,881	1162	967	227	424	7,997	1149	921		364
STILLBIRTHS	211	22	24			184	21	23		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Week Ending August 7

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 532, whooping-cough 1,710, diphtheria 18, measles 2,892, acute pneumonia 234, acute poliomyelitis 82, dysentery 324, paratyphoid fever 4, and typhoid fever 3.

Infectious Diseases

Only slight changes were recorded in the incidence of infectious diseases in England and Wales during the week ending July 31. Dysentery notifications declined by 89, from 534 to 445, scarlet fever by 73, from 785 to 712, and whooping-cough by 30, from 2,030 to 2,000. Measles notifications rose by 422, from 2,965 to 3,387.

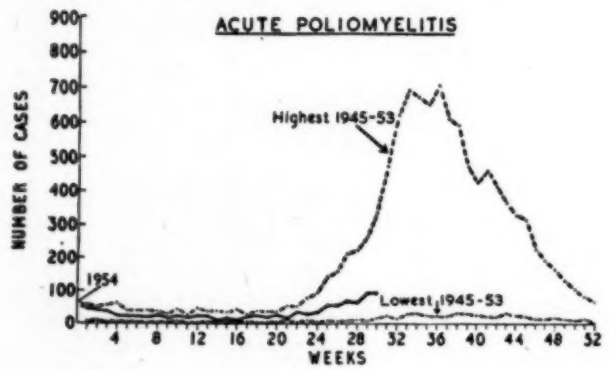
The largest variations in the trends of measles were rises of 97 in Lancashire, from 662 to 759, 34 in Essex, from 142 to 176, 32 in Norfolk, from 97 to 129, 30 in Derbyshire, from 27 to 57, and 26 in Gloucestershire, from 128 to 154. Notifications of whooping-cough rose by 26 in Leicestershire, from 30 to 56, and fell by 38 in Devonshire, from 69 to 31.

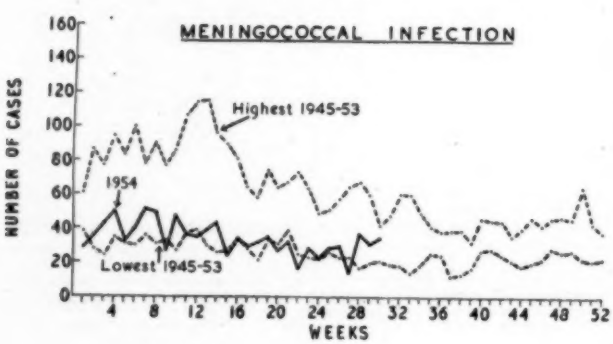
94 cases of acute poliomyelitis were notified. These were 3 fewer for paralytic and 6 more for non-paralytic than in the previous week. The largest returns were Dorset 5 (Lyme Regis M.B. 3), Durham 11 (Sunderland C.B. 8), Lancashire 8 (Liverpool C.B. 3), Middlesex 8 (Wembley M.B. 3), and Northumberland 8.

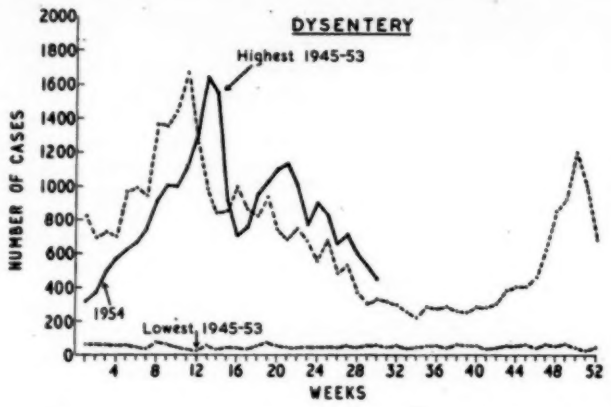
In Scotland the dysentery notifications declined sharply by 34, from 210 to 176.

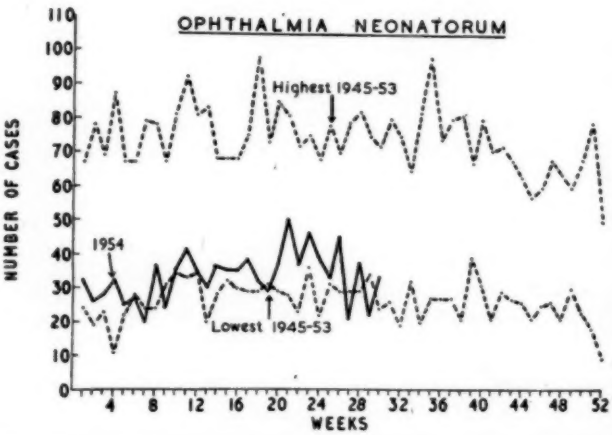
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - -, the figures for 1954 thus ————. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Medical News

World Medical Association.—At a conference in Rome on August 4, Professor A. SPINELLI, President-elect of the World Medical Association, discussed the aims and functions of the organization and drew attention to the importance of its Eighth General Assembly, which is to be held on September 26 to October 2. Professor R. CHIAROLANZA, a member of the Italian Parliament, also addressed the meeting on the subject. Representatives of the medical profession in 52 nations will meet at Rome under the auspices of the Italian Medical Federation to discuss, among other subjects, the ethical code, the medical attitude to atomic and bacteriological warfare, experiments on human beings, and the rights and duties of the profession in the field of social medicine. One session will be devoted to the medical press.

Compressed-air Illness.—An investigation into compressed-air illness during the construction of the Tyne Tunnel was carried out by Professor W. D. M. PATON and Dr. D. N. WALDER during the two years June, 1948, to July, 1950. Their report has now been published in the Medical Research Council Special Report Series, No. 281 (H.M.S.O. 5s.). They reviewed about 4,000 compressions to which 376 men were subjected; 187 of them suffered bends on one or more occasions and there were 350 cases of decompression sickness. Two resulted in permanent spinal paralysis. The bends rate fluctuated from week to week, partly in accordance with the recruitment of new labour; it appeared to decline with lapse of time. The decline was found to be due mainly to acclimatization and slightly to elimination of susceptibles. The authors suggest that the initially high rate associated with the influx of new labour could be lessened by a preliminary training. Above the age of 50 susceptibility to bends increased, but body weight was not significantly correlated with it. There seemed to be a functional element in some of the cases. The authors make

various detailed recommendations on the technique of preventing and treating compressed-air illness.

Legal Restriction Removed.—Public authorities, which term includes hospital authorities, may now have actions for damages for negligence brought against them up to three years from the event complained of. The period was formerly one year, and the alteration puts them on the same footing as private persons. It has been brought about by the Law Reform (Limitation of Actions, etc.) Act, 1954, and takes effect from June 4 last. For actions founded on simple contract or tort the limitation period is six years. Special provisions are made for persons unable to bring an action owing to a disability.

The Worshipful Company of Barbers of London.—At a meeting of the Court of Assistants of the Barbers' Company at the Royal College of Surgeons on August 12, Sir CECIL WAKELEY was installed as Master and Sir JOHN MCNEE as Renter Warden.

West London Medico-Chirurgical Society.—Dr. W. E. THROWER has been elected president for the year and will deliver his presidential address on October 21 at a dinner meeting at the Rembrandt Hotel. The title will be "The Journey from the Bench to the Bedside." The hon. secretaries of the society are Mr. K. G. ROTTER and Dr. J. F. GOODWIN, and the hon. treasurer is Mr. G. B. WOODD WALKER.

Society of Apothecaries.—Sir CECIL WAKELEY was elected Master at the annual election at the Apothecaries' Hall on August 17. The retiring Master is Dr. SEAWARD MORLEY. Dr. NEVILLE FINZI was elected Senior Warden, and Dr. MACDONALD CRITCHLEY Junior Warden.

Dr. R. J. Harrison, reader in anatomy at London Hospital Medical College, has been appointed to the university chair of anatomy tenable at that college.

COMING EVENTS

Eighth International Film Congress will be held at Rome, November 6–12. Details from the Scientific Film Association, 164, Shaftesbury Avenue, London, W.C.2.

APPOINTMENTS

BOTHWELL, PETER WILLIAM, M.B., Ch.B., D.P.H., Deputy County Medical Officer of Health and Deputy Principal School Medical Officer for the County of Oxford.

BURNS, HELEN LOVE, M.B., Ch.B., D.Obst.R.C.O.G., Surgical Registrar at University College Hospital of the West Indies.

CAMPBELL-ROBSON, L., M.B., B.Chir., F.R.C.S., D.M.R.T., Consultant Radiotherapist, United Leeds Hospitals.

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—P. F. A. Pereira, M.B., B.S., D.P.H., Assistant Physician (Geriatrics), East Suffolk and Ipswich Hospital Group; J. N. Badham, M.R.C.S., L.R.C.P., D.P.M., Assistant Psychiatrist, Little Plumstead Mental Deficiency Group of Hospitals; D. G. Sloan, M.B., B.Ch., Medical Registrar, Papworth Hospital; R. H. Browning, M.B., B.S., Medical Registrar, Peterborough Hospital Group.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Gowar.—On July 14, 1954, to Dorothy Mary (formerly Rogers), wife of F. J. Sambrook Gowar, V.R.D., F.R.C.S., of Sunninghill, Milltimber, Aberdeenshire, a son.

Kitchen.—On August 8, 1954, to Hattie, wife of Dr. Claude H. Kitchen, of Mayfield, Boldon Lane, Cleadon, Sunderland, Co. Durham, a son.

Stanger.—On August 13, 1954, to Helen (formerly Roe), wife of R. A. Stanger, M.B., B.Chir., of "Apple Trees," School Road, Bursledon, Hants, a son—Robin John.

Walters.—On August 8, 1954, at the Bromhead Nursing Home, Lincoln, to Daphne (formerly Pullein-Thompson), wife of Geoffrey A. Bagot Walters, F.R.C.S.Ed., a brother for Jennifer and Andrew.

Wilson.—On August 10, 1954, at the Christopher Nursing Home, Wigan, Lancs, to Dr. Ruth Audrey (Jane), M.B., Ch.B., wife of Bill Weatherston Wilson, F.R.C.S., a son.

DEATHS

Anning.—On August 14, 1954, James John Anning, L.M.S.S.A., of 5, Shaw Lane, Leeds, formerly of Beeston Hill, Leeds, Yorks, aged 83.

Beldon.—On August 8, 1954, in a nursing home, Harrogate, Maria Lambeth Beldon (formerly Gaunt), M.B., Ch.B., of The Mount Hotel, Leeds, and Straysyde House, Harrogate, Yorks, aged 53.

Gillespie.—On July 26, 1954, John Marchbank Gillespie, M.C., M.B., Ch.B., Surgeon Commander, R.N., retired, of 1, Bryanston House, Dorset Street, London, W.

Hillier.—On August 4, 1954, Tom Robert Ernest Hillier, M.R.C.S., L.R.C.P., of 15, Weech Road, Hampstead, London, N.W.

McArthur.—On July 30, 1954, at his home, Alexander Gordon Finley McArthur, M.B., B.Ch.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Ridding a Dairy Herd of Tuberculosis

Q.—*I have recently been very interested in the efforts of a neighbouring farmer to rid his dairy herd of reactors to the tuberculin test. Time after time he has weeded out the reactors and built up the herd again. After four years, when success seemed imminent, fresh tests picked out 20 reactors. There are two byres, and it has been invariably the case that the animals from the large byre are reactors. The farmer has been advised that the infection is acquired in this building and that he should build a new byre. Large-scale disinfection of the byre, including going over all the woodwork with a blowlamp, has met with no success in the tests. Is it possible for a building to harbour tuberculosis infection in this way? If so, is there any means of eradicating the infection without rebuilding?*

A.—It is generally recognized that farm buildings can be freed of the tubercle bacillus which has been shed by infected animals if the methods of disinfection are sufficiently drastic, and include the very thorough treatment of all woodwork by the blowlamp. This, however, does not entirely avoid the reintroduction of infection when the byre is still being used by potentially dangerous animals. It is generally recommended that, in order to be quite safe, the building should be stocked with cattle from attested herds. In this instance it would appear that the farmer has never completely freed his stock from tuberculosis by systematic tuberculin testing. This experience is not unusual and is due, of course, to the fact that when a herd test is applied and all the reactors are removed some of those which remain may be in the incubative stage of the disease, when they are tuberculin negative. They will be detected at the next test, but in the meantime one or more of them may have infected not only their neighbours but also the building which has been freed from infection by rigorous disinfection.

In regard to this particular herd, the information supplied is quite inadequate to give any opinion on whether the buildings are responsible for the maintenance of infection. We are not told whether the animals from the large byre are allowed to graze on pastures which may have been run over at some time by infected cattle. I mention this point because we know that under favourable circumstances the tubercle bacillus can remain alive on pastures for at least six months. We are not told whether cattle on the neighbouring farms are tuberculous, and, in that event, whether the fields of the farmer concerned are double-fenced to prevent the danger of contact infection; nor are we told whether there are any effluents from neighbouring farms which might contaminate the water supplies. These are just a few of the many factors which might be responsible for maintaining infection.

Perforated Ear Drum and Loud Noises

Q.—*Are sudden loud noises, as occur when shooting, harmful if the tympanic membrane is perforated? Should I advise a man who has had a successful fenestration operation to give up shooting, of which he is very fond?*

A.—Close exposure to sudden loud noises such as are experienced when shooting is always potentially harmful whether or not the tympanic membrane is perforated. Anyone who has ear trouble at all will be wise to wear a plug of wool in the affected ear when shooting. With regard to fenestration, if this has been successful, then I think it is wiser not to go shooting; but, if this advice is likely to be

disregarded, then the next best thing would be to wear a thick plug of wool or a mixture of wax and wool such as "boules quies," which are made by the Laboratoires Quies, Paris, and obtainable in England from Roberts & Co., of 76, New Bond Street, W.1.

Infolerance to Mercurial Diuretics

Q.—*What treatment is advised for a case of rheumatic congestive heart in which mercurial diuretics cause the typical gingivitis of mercurialism? Is B.A.L. or some other diuretic advised? Local treatment of the gums has not helped very much, and the dentist is loath to extract teeth which are sound.*

A.—Stomatitis and gingivitis are unusual complications of treatment with mercurial diuretics, and when they occur they are usually due either to sensitivity to the particular mercury compound in use or to inadequate elimination of mercury from the body. When due to sensitivity, a change from one mercury compound to another sometimes relieves the symptom. In the present case, however, it would seem advisable to abandon treatment with mercurial diuretics altogether. Treatment with dimercaprol (B.A.L.) is valuable in such cases, but the continued use of mercurial diuretic at the same time savours of giving a poison and its antidote together, and alternative means of relieving the oedema should be sought. A strict low-sodium diet should be given, and digitalis, if not already in use, might be of value. Perhaps the best diuretic in cases intolerant to mercury is urea. Urea is a safe and efficient diuretic provided that renal function is good and the dose of urea is adequate. It should be given in doses of 10 g. three times daily and increased to 20 g. three times daily, but periodic estimation of the blood urea should be done. Relief of oedema by mechanical means has become a much more practical procedure since antibiotics became available to control the infections which so commonly complicate this method of treatment. Southey's tubes should be inserted in the legs after the patient has been kept in the sitting posture until most of the oedema has gravitated to the lower half of the body.

Therapeutic Abortion or Sterilization for Rh Incompatibility

Q.—*A woman has had a series of stillbirths due to Rh incompatibility. She is Rh-negative and the husband Rh-positive homozygous. Is this legitimate grounds for carrying out (a) therapeutic abortion in the event of a further pregnancy, or (b) sterilization?*

A.—Opinion in regard to Rh incompatibility has to some extent changed in recent years, and the outlook for a baby whose mother is sensitized to Rh antigen is not regarded as being so unfavourable as previously. It is now known that in circumstances such as those described, and even though a woman has already had two or more grossly affected dead babies, it is not inevitable that a subsequent child will not survive. The chance of survival may be small, but cases are described. The finding that a husband's blood is homozygous Rh positive is apparently not always reliable, even when the investigation has been carried out by experts in the field. In the case in question, therefore, it may well be decided to terminate an early pregnancy on the grounds that the chance of an unaffected child is flimsy, and that the mental stress involved in allowing the pregnancy to continue would be detrimental to the mother's health, but before the decision is taken it should be clear to all concerned that the outlook for the child is not completely hopeless.

When it comes to the sterilization of an Rh-sensitized woman the problem is even more difficult because this is an irrevocable step. Before it is undertaken the medical practitioner and the patient and her husband should realize: (1) that despite the bad history the subsequent birth of a healthy child is not impossible even though it is improbable; (2) the husband, although apparently homozygous, may really be heterozygous and may ultimately father an Rh-negative child; (3) the husband may die and the wife might then remarry an Rh-negative man and wish to have children by him; (4) a means of prevention or cure of haemolytic disease of the foetus may be found at any time in the future.

Contraception is therefore usually preferable to sterilization, and if, perchance, it should fail therapeutic abortion could always be considered unless, in the meantime, advances in knowledge ensure protection of the foetus.

Two easily available references which deal with these particular aspects of this difficult subject are Chapter 12 by P. L. Mollison in *Modern Trends in Obstetrics and Gynaecology*, by K. Bowes (London, Butterworth, 1950), and Chapter 4 in *Recent Advances in Obstetrics and Gynaecology*, by A. W. Bourne and L. H. Williams (London, Churchill, 1953). Both these authorities state that the circumstances outlined in this question do not warrant sterilization, although Mollison at least points out that there may be a place for therapeutic abortion in individual pregnancies in certain cases.

Indications for Massage

Q.—*Massage seems to be falling out of favour nowadays, being largely replaced by active movements and electrical treatments. Why is this? What are the main indications for massage?*

A.—In the last twenty years the concept of physiotherapy has changed considerably. Whereas previously treatment was mainly passive and palliative, nowadays the emphasis is on activity and rehabilitation; hence the decline in the use of massage and the increase in the use of active movements and exercises. Electrotherapy is also falling into eclipse.

Massage has four useful functions: (1) By bringing about relaxation of muscles it relieves pain due to muscular spasm. (2) By relieving spasm it is a useful preliminary to other and more active forms of treatment. (3) In the form of frictions it can bring about the resolution of a post-traumatic inflammatory lesion, provided that the lesion is localized and superficially placed, as, for example, in a tennis elbow or ankle strain. (4) By softening the induration in the floor and tissues surrounding chronic varicose ulcers it often leads to healing of the ulcer.

Laboratory Tests for Syphilis

Q.—*Is there any quick and reliable substitute for the Wassermann and Kahn reactions in the diagnosis of syphilis?*

A.—Routine serological tests for syphilis consist of complement-fixation tests (Wassermann), precipitation tests (Kahn, V.D. Research Laboratory, Price's precipitation reaction), and clarification tests (Meinicke). None of these tests should be performed except by trained and skilled workers. There are no quick and reliable substitutes, and the choice of tests is determined by personal preference and the conditions under which the work has to be done.

Refresher Course Books.—The first two volumes of collected articles from the Refresher Course for General Practitioners published in the *Journal* are now available. The first volume contains 55 articles and the second 60. Each article has been revised by its author. Copies of both volumes may be obtained, price 25s. (postage 1s.) each, direct from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or from booksellers. The second book of **"Any Questions?"** is also available, price 7s. 6d. (postage 6d.).

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